INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	DEBIKA DATTA
Roll Number	:	136106018
Programme of Study	:	Ph.D.

Thesis Title: Tailoring Short Self-Assembling Peptides into Biocompatible Gelators

Name of Thesis Supervisor(s)	:	Dr. NITIN CHAUDHARY and Dr. VIBIN RAMAKRISHNAN
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SHORT ABSTRACT

The thesis largely focuses on the self-assembly of designed amyloidogenic and fatty-acylated peptides and their potential applications in healthcare. The short amyloidogenic-stretch of β-amyloid, $A\beta_{16-22}$ (Ac-KLVFFAE-am), is a useful model peptide to study the aspects of β-amyloid fibril formation. Herein, the self-assembly was investigated by incorporating β-turn-inducing motifs (Asn-Gly, ^{D}Pro-Gly, and Aib-^{D}Pro), in the Ac-KLVXZAE-am chains, where X and Z are the aromatic amino acids, Phe, Tyr, or Trp. The peptides harboring β-turn-inducing motifs aggregate rapidly, cause substantial enhancements in thioflavin T (ThT) fluorescence compared to the controls, the β-turn motif-lacking peptides. The thesis also discusses the theoretical results obtained from molecular dynamics simulation of the turn-containing peptides, giving insights into the type of turn formed. A follow-up investigation into the amyloidogenic propensity showed that the aromatic analogue AβFY (Ac-KLVFYAE-am) and $A\beta_{16-22}$ repeats (specifically the ones having Phe-Phe or Phe-Tyr aromatic cassette in their sequence) connected through Asn-Gly, Aib-^{D}Pro, and ^{D}Pro-Gly forms self-supporting soft gels at concentrations ≥2 mM, even though the end-capped parent peptide does not form hydrogel up to 20 mM (1.8% w/w) concentration in 10% HFIP. The study delves into the characterization and possible applications of the hydrogel. The hydrogels made up of amyloid-like fibers possess distinct elastic properties. The gel is shown to support the growth of rat pancreatic cells (RIN-5F), human embryonic kidney cells (HEK-293), baby hamster kidney cells (BHK-21), and human neuroblastoma cells (IMR-32). The results include the doxorubicin release assay showing its potential as a drug-delivery vehicle, the thermal/mechano response of the gels, as well as the gelation at the acidic pH. To gain insights into the folded conformation, investigation of the β-turn-supporting motifs was also carried out using proton NMR spectroscopy (1H, TOCSY and NOESY). Individual amino acids or pairs of amino acids such as AA, KK, LL, VV, Aromatic-Aromatic, EE, could be unambiguously identified. The data, was interpreted using the chemical shift indices and indicated turn formation. Despite their potential in diverse applications, high production cost limit their commercialization for the above hydrogels. Keeping this in mind, another set of peptides wherein the peptidic chain contained rather inexpensive amino acids viz. Val, Leu, and Ile

coupled with 3 fatty acids (Palmitic acid, Myristic acid, Lauric acid), was designed, synthesized, and their gelation potential investigated. Out of the 27 fatty-acylated peptides, 8 resulted in distinct water-alcohol gels. The 2 wt% gels can entrap the hydrophobic anticancer drug, docetaxel causing sustained release for 3 days in PBS. Such bigels can find applications in the delivery of drugs that have low solubility in water and therefore tend to precipitate in the hydrogels.