The proteins we observe in nature undergo proper folding to impart biological functions. If proteins misfold, cellular pathways recognize and degrade the misfolded proteins thus inhibiting them from causing any impairment. If a cell fails to degrade misfolded proteins, it may form aggregates which can progress to amyloids thus leading to several neurodegenerative diseases. Dementias are responsible for the greatest burden of neurodegenerative diseases. Alzheimer's disease (AD) is one of the most common forms of progressive irreversible dementia representing approximately 60-70% of dementia cases, affecting large numbers of elderly Worldwide. With the advancement of the disease, patient suffering from AD starts having problems including: memory loss, mood and personality changes, inability to communicate, increased anxiety and/or aggression, and taking longer time to complete normal daily tasks. As the patient's condition deteriorates bodily functions are lost, ultimately leading to death. The life span of people with AD is greatly governed by the age of the person when the disease is diagnosed.

Like other neurodegenerative diseases AD is characterized pathologically by the accumulation of amyloids plaques. The major constituent of amyloid plaque is found to be Amyloid β (Aβ) peptide which is generated from the sequential cleavages of amyloid precursor protein (APP). This Aβ peptide exists in two isoforms, $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide. Among the two isoforms, the aggregation of $A\beta_{1-42}$ is found to be more significant and toxic. $A\beta_{1-42}$ peptide has the propensity to misfold into β-sheets and aggregate to form neurotoxic oligomers and eventually mature amyloid fibrils.

Many experimental studies like Nuclear magnetic resonance spectroscopy (NMR), X-ray crystallography, Circular dichroism (CD), ion mobility mass spectrometry (IM-MS), electron microscopy (EM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) measurements have been carried out to investigate and elucidate the initial seed structure of $A\beta_{1-42}$ peptide that triggers aggregation. Despite a high degree of sophistication, probing the conformational changes of $A\beta_{1-42}$ peptide aggregation is challenging owing to the vast heterogeneity of the aggregates and the sensitivity of the process to different environmental conditions. The wide availability of alternative homologous peptide conformations, stringent regulation of experimental parameters and the comparatively shorter duration for the analysis of desired protein sequences have facilitated a major shift towards the current use of computational tools. Thus, in order to characterize the structural features of the

probable initial seed structure of $A\beta_{1-42}$ peptide responsible for aggregation we used fully unrestrained molecular dynamics (MD) folding simulations. We have initiated the simulation of $A\beta_{1-42}$ peptide with its extended initial linear conformation built from its amino acid sequence and charted down the development of secondary structures. Our findings showed formation of extensive β-strands at specific regions of $A\beta_{1-42}$ peptide.

During the initial stage of aggregation each monomer of $A\beta_{1-42}$ peptide interacts with its adjacent monomer to form dimer. Thus, a dimer provides the first opportunity to investigate the inter-molecular interactions that lead to the formation of toxic aggregates. However, the structural characterization of $A\beta_{1-42}$ peptide dimer at the atomistic level and the dimerization mechanism by which $A\beta_{1-42}$ peptides co-aggregate still remains not clear. Thus, it is necessary to investigate the course of $A\beta_{1-42}$ peptide dimerization which is known to play an important role in the plaque formation. Accordingly, we carried out potential of mean force (PMF) analysis to study the dimerization mechanism of $A\beta_{17-42}$ peptide, which was computed as a function of inter-chain distances between the entire C-α atoms of the monomers. Since $A\beta_{17–42}$ peptide is a key fragment of $A\beta_{1-42}$ peptide, the formation of its U-shape protofilament is likely to be very similar to that of $A\beta_{1-42}$ peptide. The $A\beta_{17-42}$ monomeric units were specifically shown to have an increased β-strands propensity at the hydrophobic regions encompassing the Central Hydrophobic Core (CHC) region and the simulation studies show this hydrophobic region to be crucial in dimerization.

The two pathological hallmarks associated with AD include the accumulation of senile plaques and the generation of neurofibrillary tangles (NFTs) by Tau. Although it is a known fact that interaction of Tau with $A\beta_{1-42}$ peptide oligomers could destabilize the microtubule integrity and might lead to the formation of new aggregates, there is no reasonable explanation for the $A\beta_{1-42}$ peptide and Tau interaction in particular. So, we have used MD simulation with the umbrella sampling (US) simulations to examine the cross-sequence interactions between homo-dimers and the hetero-dimer of $A\beta_{25-35}$ peptide and $Tau_{273-284}$ by computing PMF. Various bonding and non-bonding interactions along with interface residues and interface areas on the early events of the peptide self-assembly was also investigated. The results indicated $A\beta_{1-42}$ peptide to have a high affinity to form dimer complex with Tau which consequently advances to form aggregates. Furthermore, we used disorder predictors AMYLPRED2 and DisEMBL to

identify the disordered regions in $A\beta_{1-42}$ peptide. We found $A\beta_{1-42}$ peptide to have disordered regions in the CHC region and C-terminal region.

While oligomers such as trimers and tetramers are the most critical players in the pathology of AD and fibril fragmentation are toxic as well, there is currently little information in atomistic level and the dynamics of their assembly. Atomistic characterizations of the $A\beta_{1-42}$ peptide oligomers are still at a difficult phase owing to their highly aggregation-prone propensity and tend to degenerate by displaying multiple polymorphic structural variants. Earlier studies have reported that the synthetic $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide isoforms can polymerize through distinct pathways. However, a full dynamic and thermodynamic picture of the interactions of the individual monomeric units to form an oligomer is very difficult. Consequently, to better understand the molecular interactions of $A\beta_{1-42}$ peptide oligomers, we have performed MD simulations on the trimer and tetramer structures of full-length $A\beta_{1-42}$ peptide and have analyzed the forces that drive the oligomerization. From the interaction studies, we found that inter-peptide salt bridges, hydrogen bonds and non-bonded contacts play a pivotal role in the stabilization of the oligomers. The structural changes in $A\beta_{1-42}$ peptide lead to various β-sheet containing structures that eventually self-assemble and result in different polymorphic oligomers, and fibrils. These polymorphic structures of $A\beta_{1-42}$ peptide perhaps induce the difficulty in understanding the pathological mechanism of AD. In this context, we have carried out interaction studies on the $A\beta_{1-42}$ fibril polymorphs. Thus our interaction study proved CHC region and C-terminal region played an important role in the aggregation of $A\beta_{1-42}$ peptide.

Although there is no cure to AD, a large number of potential Aβ fibrillogenesis inhibitors have been suggested. Significant efforts have been made to find drugs to combat with this disease. Consequently, we have also demonstrated different approaches to inhibit the aggregation of $A\beta_{1-42}$ peptide at early and later stage. We have used: (i) ss- oligonucleotide; (ii) an isoform of $A\beta_{1-42}$ peptide, $A\beta_{1-40}$ peptide and (iii) 6-mer peptide (IGLMVV) as potent inhibitors in the aggregation process of $A\beta_{1-42}$ peptide. We found ss-oligonucleotide to encapsulate the $A\beta_{1-42}$ peptide thereby preventing the dimer formation. Additionally, ss-oligonucleotide was found to facilitate the disassembly of $A\beta_{17-42}$ dimer. In presence of $A\beta_{1-40}$ peptide, the β-content of $A\beta_{1-42}$ monomer was reduced. Likewise, we have also used 6-mer peptides as potent inhibitor of $A\beta_{1-42}$ peptide aggregation. The MD simulation results of the 6-mer peptide

(IGLMVV) and fibril complex showed the inhibitory effect of the peptide by dissociation of the fibril to single strands.