## Structural studies and neurotoxic effects of a soluble oligomer of the amyloid beta peptide fragment (22-35) with the D23N Iowa mutation

Various natural mutations in Alzheimer's β-amyloid peptides (Aβ) (39-43 residues) have been shown to promote an early-onset of Alzheimer's disease (AD). Most mutations promote amyloid fibril formation of Aβ and exhibit neurotoxicity. Recent studies demonstrated that the *Iowa* mutation (D23N) enhances neurotoxicity of 40-residue Aβ(1-40) and 42-resdue Aβ(1-42) while promoting formation of subfibrilliar intermediates rather than fibrils. In spite of the unique properties of the Iowa mutant and various kinetic studies, little experimental evidence has been obtained about structures of the **intermediate species** for this mutant. Our interest is a shorter (14 residue) fragment of the Aβ. The 22-35 residue was chosen because residues 10−22 and 30−40 are separated by a non-β-sheet "bend region" which appears from solid-state NMR and other indications to be an ordered structure and a salt bridge occurs between the side chains of Asp23 and Lys28. Most Aβ mutations associated with familial AD occur at or near this bend region, in residues 21−23. Tycko recently showed that folding of the bend region is a critical or rate-limiting step in the fibrillogenesis of at least one form of Aβ fibrils. We studied the misfolding kinetics of the D23N mutant for 14-residue Aβ peptide in order to examine the possibility of isolating the intermediates for structural studies by nuclear magnetic resonance (NMR). The intermediate species in the course of fibril formation of D23N was detected by multiple methods such as UV/Vis, IR, and fluorescence spectroscopy.