Abstract Submitted
for the MAR11 Meeting of
The American Physical Society

Early aggregation studies of diabetic amyloid in solution
SADANAND SINGH, JUAN DE PABLO, University of Wisconsin-Madison — Islet amyloid polypeptide (IAPP, also known as amylin) is responsible for pancreatic amyloid deposits in type II diabetes. The deposits, as well as intermediates in their assembly, are cytotoxic to pancreatic β-cells and contribute to the loss of β-cell mass associated with type II diabetes. To better understand the mechanism and cause of such aggregation, molecular simulations with explicit solvent models were used to compare monomer structure and early aggregation mechanism. Using free-energy maps generated through a variety of novel, enhanced sampling free-energy calculation techniques, we have found that, in water, the peptide adopts three major structures. One has a small α-helix at the N-terminus and a small β-hairpin at the other end. The second and the most stable one, is a complete β-hairpin, and the third is a random coil structure. Transition Path Sampling simulations along with reaction coordinate analysis reveal that the peptide follows a "zipping mechanism" in folding from α-helical to β-hairpin state. From studies of the dimerization of monomers in water, we have found that the early aggregation proceeds by conversion of all α-helical configurations to β-hairpins, and by two β-hairpins coming together to form a parallel β-sheet. Several aspects of the proposed mechanism have been verified by concerted 2D IR experimental measurements, thereby adding credence to the validity of our predictions.

Sadanand Singh
University of Wisconsin-Madison

Date submitted: 19 Nov 2010 Electronic form version 1.4