Structural Studies of Alzheimers beta-Amyloid Fibrils

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Research Abstract
Progress in FY2016 has been in the following areas: (1) AMYLOID FIBRIL STRUCTURES DERIVED FROM BRAIN TISSUE: In collaboration with Prof. John Collinge of University College London, we have obtained solid state NMR and electron microscopy data for fibrils derived from 37 brain tissue samples from autopsies of AD patients in four categories (typical long history, posterior cortical atrophy, short duration, nondemented). Using our published amyloid extraction and seeding protocols, isotopically labeled fibrils were prepared using both 40-residue and 42-residue amyloid-beta peptides. The solid state NMR data suggest that most AD patients

develop the same predominant 40-residue fibril structure in their brains, but that short duration patients can develop different and more heterogeneous structures. Results for 42-residue fibrils indicate no clear correlation between patient category and molecular structure. We have now completed the analysis of these data and submitted a manuscript for publication. After the first round of reviews of this manuscript, we performed additional data analyses and additional control experiments. We await a final decision from the journal. In these studies, we find one predominant 40-residue amyloid-beta fibril polymorph, and two predominant 42-residue fibril polymorphs. We have not yet developed full molecular structural models for these predominant polymorphs. This will be a goal for future studies. It will also be important to test the capacity of these polymorphs to “”cross-seed”” one another. (2) ADSORPTION OF AMYLOID-BETA PEPTIDES INTO SEEDED GELS: AD is generally believed to result from aggregation of amyloid-beta peptides in brain tissue. Amyloid-beta aggregation depends on supersaturation, i.e., on the development of amyloid-beta concentrations that exceed equilibrium solubility levels in the tissue. We are exploring an approach to remove excess amyloid-beta from fluids, by introducing hydrogel particles that contain amyloid-beta fibril seeds. Preliminary experiments show that amyloid-beta peptides diffuse into the gels and add to the seeds until the peptide levels in the surrounding fluids drop close to the equilibrium solubilities. Results from these experiments will be submitted for publication soon.

Further information available at:

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