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Structural Characterization of Amyloid Fibrils Using Deep UV Raman Spectroscopy

DESCRIPTION (provided by applicant): Amyloid fibrils are associated with numerous debilitating diseases such as Alzheimer's disease, Parkinson's disease, Huntington's diseases, prion disease, familial amyloid polyneuropathy, senile systemic amyloidosis and type II diabetes, etc. The rational design of successful therapeutic strategies calls for detailed structural characterization of amyloid fibrils. Solid-state NMR and X-ray microcrystallography applied to short peptide fragments of amyloidogenic proteins have contributed greatly to our knowledge about the fibril core structure. The main goal of this project is to extend our understanding of the amyloid fibril structure by utilizing deep ultraviolet resonance Raman spectroscopy combined with hydrogen-deuterium exchange. This new method, recently pioneered in our laboratory, does not require isotope labeling and creates the opportunity for bridging the gap between our extended knowledge in the structural variations of model short peptide microcrystals and the core structure of amyloid fibrils prepared from entire proteins. We will determine and classify the core structure of amyloid fibrils prepared from full-length proteins. It has been postulated that differences in infectivity of prion protein aggregates, and related differences in the apparent symptoms of Creutzfeldt-Jakob disease patients, are possible due to amyloid polymorphism. Small molecules could potentially manipulate aggregate morphology and provide the basis for therapeutic approaches to suppress the formation of toxic aggregates. Therefore, it is critical to (i) have a robust method for structural characterization of polymorphs, (ii) understand the nature of amyloid polymorphs and their toxicity, and (iii) eventually, be able to control (suppress) the formation of toxic polymorphs. We will test alternative hypothesis concerning the level of structure at which functional polymorphisms are realized. When fully developed, in future studies, the proposed approach will make possible the comparative structural characterization of in vivo and in vitro amyloid fibrils. This will bridge the gap between in vivo and in vitro studies of neurodegenerative diseases. In particular, the method will provide unique information revealing the structural determinants of infectious and non-infectious amyloids.

PUBLIC HEALTH RELEVANCE: Successful outcomes of the proposed study will not only improve our understanding of amyloid fibril structure in general and the nature of amyloid polymorphs and their toxicity in particular, but also provide the basis for the development of therapeutic approaches to suppress the formation of toxic aggregates. When fully developed, the proposed approach will make possible the comparative structural characterization of in vivo and in vitro amyloid fibrils and bridge the gap between in vivo and in vitro studies of neurodegenerative diseases.