Tau - a natively unfolded protein: Structure and prevention of pathological conformations in Alzheimer's disease

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Tau is a neuronal protein important for microtubule stabilization during axonal growth and brain development. The protein is structurally unusual in that it adopts a "natively unfolded" state. In human brain tissue, tau can aggregate into "paired helical filaments" (PHF) which represent a hallmark of Alzheimer's disease and related neurodegenerative "tauopathies". It is proposed to analyze the structure of tau by NMR-based methods, identify different conformations on the way from the soluble monomer to the insoluble fibril that underlie the pathological aggregation. It is planned to synthesize and optimize compounds that interfere with the different conformations on the aggregation pathway and relate the in vitro results obtained from the structural biology work with in vivo results from cell and animal models of tau pathology. The aim of the project is to contribute to the understanding of the neurofibrillary pathology of Alzheimer's disease on the molecular and cellular level and to explore approaches to interfere and preferably prevent pathological conformation and aggregation.

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