Investigation of the relationship between the material properties of insoluble, protein aggregates known as amyloids and common forms of age-related dementia such as Alzheimer’s and Parkinson’s.

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Investigation of the relationship between the material properties of insoluble, protein aggregates known as amyloids and common forms of age-related dementia such as Alzheimer’s and Parkinson’s.

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Research Abstract
The conversion of normally soluble and functional proteins into insoluble protein aggregates known as amyloids are linked to more than 50 human disorders, including several common forms of age-related dementia such as Alzheimer’s and Parkinson’s diseases. Amyloids exist as long, rope-like structures known as fibrils which can self-associate into intractable plaques-a hallmark of many amyloid-related diseases. Here we propose to investigate the potential role the material properties of amyloid, in particular their rigidity and propensity to break, play in both the pathology and transmission of amyloid-related disorders. We propose to study the material properties of amyloid using a new and ground-breaking form of microcopy known as 4D ultrafast electron microscopy (UEM). This unique microscope combines the spatial resolution of electron microscopy (nanometer) with the temporal resolution of laser spectroscopy (femtoseconds) and can directly apply minute (piconewton) forces to materials, making atomic-scale “movies” of the resulting displacements. This sets it apart as the technique of choice for characterizing the stiffness and fracture mechanics of proteinaceous nanofibrils such as amyloid. Using this revolutionary technique, we hope to determine the stiffness of amyloids, use amyloid as a single molecule biosensor, perform optical trapping experiments on individual Alzheimer’s disease-related fibrils within the column of an electron microscope and study the destruction of cataract-related amyloid plaques. These results will provide us with some fascinating insights into the molecular forces governing the behavior of amyloids and how this may relate to their pathology in living organisms.

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