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Amyloid at the nanoscale: AFM and single-molecule investigations of early steps of aggregation and mature fibril growth, structure, and mechanics[1]

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Misfolding and aggregation of proteins into nanometer-scale fibrillar assemblies is a hallmark of many neurodegenerative diseases. We have investigated the self-assembly of the human intrinsically disordered protein alpha-synuclein, involved in Parkinson's disease, into amyloid fibrils. A particularly relevant question is the role of early oligomeric aggregates in modulating the dynamics of protein nucleation and aggregation. We have used single molecule fluorescence spectroscopy to characterize conformational transitions of alpha-synuclein [1], and to gain insights into the structure and composition of oligomeric aggregates of alpha-synuclein [2]. Quantitative atomic force microscopy [3, 4] and nanomechanical investigations [5, 6] provide information on amyloid fibril polymorphism and on nanoscale mechanical properties of mature fibrillar species, while conventional optical and super-resolution imaging have yielded insights into the growth of fibrils and into the assembly of suprafibrillar structures.

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