

## **Nanotechnological methodologies towards the discovery of the mechanisms that trigger protein aggregations associated to neurodegenerative disorders**

Neurodegenerative disorders are associated with protein aggregation. Considerable evidence indicates that along these aggregation processes the small oligomeric species are the most neurotoxic, and that their toxicity is strictly dependent on their structures. The proteins involved in these diseases are conformationally heterogeneous and, according to an emerging view, these proteins can switch back-and-forth between functional and various amyloidogenic conformations. Characterizing the monomer conformational space is critical to understand the mechanisms that trigger the formation of the oligomeric species. However, the characterization of the conformational heterogeneity of monomeric natively disordered proteins by standard structural biological methods has proven to be extremely challenging. The problem of how to characterize the conformational equilibria of natively disordered proteins associated with neurodegenerative diseases necessitates the use of novel approaches and technologies. We have recently demonstrated that a nanotechnological methodology based on the Atomic Force Microscopy capability to manipulate single molecules can be used to study the conformational properties of unfolded or partially-folded proteins (1-3). The same Atomic Force Microscopy in its imaging mode can also make it possible to "see" the aggregation processes from the monomeric to the fibrillar states, to monitor the structure of the different species and to follow the kinetics of their formation (4,5). Single-molecule methodologies thus offer exciting opportunities to increase our understanding of the conformational equilibrium of a natively disordered protein, and on this basis to drive the tailoring of new pharmaceutical strategies capable to target the most neurotoxic very early stages of protein aggregation processes.