P-1.49

Investigation of Huntingtin Conformations and Folding Dynamics

Morten Mosbach [1], Simon Ebbinghaus [1]

[1] Ruhr-University Bochum, Bochum, Germany

The protein Huntingtin is known for causing Huntington´s Disease (HD), a neurodegenerative disorder. An expansion of the Poly-Glutamine stretch present in exon-1 of Huntingtin can result in aberrant folding events. Misfolding and subsequent aggregation drive the formation of intracellular inclusions found also in tissue samples from HD patients. Those inclusions display diverse biophysical properties and their exact molecular build-up and biological function remain unknown. We are investigating folding events of the Huntingtin protein by applying single molecule based techniques such as smFRET, to decipher the molecular basis for these misfolded proteins. We want to decipher the structure of the proteins and how this links to the consequent aggregation. Previous work could already show a temperature-induced collapse of the Huntingtin protein. We want to analyze the contribution of the different exon-1 domains towards those temperature-induced collapses in vitro and in vivo. We also want to further characterize the influence of chaperones on the Huntingtin conformations and the biophysical properties of the resulting aggregates. Understanding the origin of the intracellular inclusions in a deeper way results in a better understanding of the pathological processes and might therefore open doors towards new treatment options and pharmaceutical intervention points.