

Structure dynamics and kinetics of folding and recognition in proteins by NMR

S. Prathihar¹, C. Smith^{1,2}, J. Reddy¹, T.M. Sabo¹, L. Wong¹, L. Russo¹, J. Kühn³, S. Pirkuliyeva³, D. Lee¹, T.M. Sabo¹, S. Ryzanov^{1,4}, L. Antonschmidt^{1,4}, A. Martinez Hernandez⁵, H.Y. Agbemenyah⁶, S. Shi⁷, A. Fischer⁶, G. Eichele⁵, D. Lee¹, S. Becker¹, A. Leonov^{1,4}, R. Benz⁸, M. Zweckstetter^{1,4}, J. Wienands³, A. Giese⁷, and C. Griesinger^{1,4}

¹Dept. for NMR-based Struct. Biology, Max-Planck Institute for Biophysical Chemistry, ³Institute of Cellular and Molecular Immunology, Georg August University of Göttingen, Göttingen, ⁴DFG-Center for the Molecular Physiology of the Brain, Göttingen, ⁵Genes and Behavior Dept., Max-Planck Institute for Biophysical Chemistry, Göttingen, ⁶European Neuroscience Institute Göttingen, ⁷Center for Neuropathology and prion research, LMU, Munich, Germany, ⁸ Jacobs University of Bremen, Germany, cigr@nmr.mpibpc.mpg.de

Kinetics of protein dynamics will be discussed on examples of folded on unfolded proteins [1]. Protein recognition will be described with a new mathematical method to distinguish conformational selection and induced fit [2] which includes a concept for the measurement.

Further, the role of partially disordered proteins in droplet formation is investigated. The adaptor protein SLP65 which interacts with CIN85 [3]. The two proteins are essential for B cell activation. The protein is found to be mainly unstructured and its various segments entertain different functions or interact with membranes, SH3 domains and forming coiled coils. Based on the structures, a molecular lego will be described that reduces the SLP65/CIN85 interaction to its absolutely necessary essentials. The two proteins can perform phase separation which is related to function.

We are additionally interested in a class of IDPs that are important in neuro- and cellular degeneration, which form oligomers and fibrils. Interference with these aggregates specifically on the oligomer level proves to be a valid concept for treatment of devastating diseases such as Parkinson's, Alzheimer's, Creutzfeldt Jacob disease and Type II diabetes mellitus [4]. Surprising links to some cancers can be identified which will be also be discussed in the lecture [5].

References

- [1] - C. Smith et al. *Proc. Natl. Acad. Sci. USA*. 113, 3296-74 (2016); C. Smith et al. *Angew. Chem. Int. Ed.* 54, 207-10 (2015).
- [2] - F. Paul and T.R. Weikl, *Plos Computational Biology*, 2016. **12**(9).
- [3] - M. Engelke et al. *Science signaling*: 7 (339) ra79 (2014); J. Kühn et al. *Science signaling*: 9 (434) ra66 (2016).
- [4] - C.W. Bertocini et al. *PNAS* 102, 1430-1435 (2005); P. Karpinar et al. *EMBO J* 28, 3256-3268 (2009); J. Wagner et al. *Acta Neuropath.* 125, 795-813 (2013); A.A. Deeg, *Biochim. Biophys. Act.* 1850 (9), 1884-1890 [2015]; S. Shi, *J. Neuropath. Exp. Neurol.* 74(9) 924-933 (2015); J. Wagner et al. *Act. Neuropath.* 130, 619-631 (2015).
- [5] - E. Turriani, et al. *Proc. Natl. Acad. Sci. USA* 114, E4971-E4977 (2017).