NOVEL HIGH-RESOLUTION STRUCTURAL MODELS OF MEMBRANE BOUND α-SYNUCLEIN

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α-synuclein (αS) is an intrinsically disordered protein (IDP) important in neurodegenerative disorders such as Parkinson's disease and Lewy body dementia.[1] It can adopt a large array of varying structures, some of which can form toxic aggregates.[2] These aggregates interact with cellular membranes and can disrupt them, leading to their incorporation in Lewy Bodies.[3] Despite regulated interaction with the membrane being crucial for αS functionality[4] the interaction has been shown to promote aggregation *in vitro.*[5] Although, high-resolution structural information has been obtained in the SDS-micelle bound state,[6] deriving structures from membrane bound αS has been hindered by the large variation in the structural ensemble and lower resolution techniques have indicated differing states of the protein and the oligomers it forms on membranes.[7,8] To obtain new insight into the structural parameters of membrane bound αS, we combine the use of NMR derived parameters obtained on SDS-micelle and bicelle bound αS with chemical crosslink mass spectrometry (XLMS) on $^{14}N/^{15}N$-labelled α-synuclein mixtures. In contrast to the available micelle bound structure, which focused on the use of nuclear Overhauser effects (NOEs) and residual dipolar couplings (RDCs),[6] our data relies predominantly on paramagnetic relaxation enhancements (PRE) and interference (PRI) measurements for long-range information. These measurements are very sensitive to compact substates of the ensemble, allowing us to detect novel conformations in the membrane bound ensemble of αS. We validate our findings by cross-checking the modeled structures with data obtained from XLMS and discuss their relevance in the context of known mutations and regions relevant for oligomer formation.

Acknowledgements. This work has been supported by UCB Biopharma SRL, the Christian Doppler Laboratory for High-Content Structural Biology and mass spectrometry measurements were performed using the Vienna BioCenter Core Facility instrument pool.

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