Inhibition Of Alpha-Synuclein Aggregation

Nikolai Lorenzen
Protein Biophysics Group, Interdisciplinary Nanoscience Center (iNANO)
Department of Molecular Biology, University of Aarhus
Gustav Wieds Vej 10C, DK - 8000 Aarhus C
E-mail nikolai@inano.au.dk

The intrinsically disordered protein alpha-synuclein (aSN) is perhaps the best validated target for Parkinson Disease (PD). It self aggregates into large protein complexes that in turn lead to lewy bodies, one of the hallmarks of PD. Hence stopping the aggregation of this protein is a recognized strategy for developing disease modifying agents. An intriguing property of aSN is the ability to interact with membranes both in monomeric and oligomeric form, where especially the ladder specie is believed to be the cause of the toxicity of aSN in PD.

In this project we are following up on a primary screening of approximately 750.000 compounds where 150 were identified as potential candidates (hits) for inhibiting the aggregation of aSN. This stage is a comprehensive secondary screening initially focussing on the following aspects:

1. Effect on the membrane permeabilizing ability of aSN oligomers.
2. Ranking of the hits to identify the most anti-aggregation compounds.
3. Measurement of binding affinity to monomeric and oligomeric aSN

The most promising candidates will be passed on for external colaborators to perform a cell-based tertiary screening . In parallel we will investigate the underlying mechanisms of the hits ability to inhibit aggregation and to alter the membrane affinity of aSN. This study will be three-dimensional, using our in house mutant library of aSN, tryptophan variants will be coupled with fluoroscence techniques and cysteine mutants will be set for electron paramagnetic resonance and furthermore we will use small angle x-ray scattering.