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# Topical Seminar

## Patient cerebrospinal fluid derived αSynuclein fibrils from Parkinson's Disease and Multiple System Atrophy have different folds and cellular inclusion pathology

Aggregation of α-synuclein (αSyn) fibrils is linked to neurodegenerative synucleinopathies, including Parkinson's disease (PD) and Multiple System Atrophy (MSA). αSyn fibrils exhibit disease-specific structural polymorphisms, with three main types characterized so far: *in vitro*, brain-derived (*ex vivo*), and brain-seeded fibrils. Although brain-derived fibrils are the structural benchmark, they are only accessible post-mortem. As a non-invasive alternative, cerebrospinal fluid (CSF)-derived fibrils offer potential for early diagnosis. CSF-seeded fibrils, amplified via seed amplification assays (SAA), resemble brain-derived fibrils but lack high-resolution structural characterization. To address this, we used SAA to amplify uniformly $^{13}C$,$^{15}N$-labeled αSyn from CSF of PD and MSA patients, enabling detailed structural analysis. Solid-state NMR and cryo-EM revealed disease-specific fibril folds. PD fibrils showed two polymorphs: helical (~60%) and straight (~40%), while MSA fibrils formed only straight filaments (100%). HDX-MS further mapped solvent accessibility differences. Notably, CSF-derived fibrils differed significantly from brain-derived and seeded fibrils, broadening the known αSyn structural diversity. These insights highlight the need for disease-specific studies to better understand pathogenic mechanisms and guide targeted therapies for synucleinopathies.

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Date: **Thursday 12 June 2025**
Time: **13:00 – 14:00**
Venue: **1170 - 347**
Address: **Ole Worms Allé 3, 8000 Aarhus C**

**OPEN TO ALL INTERESTED.**

**Host:** Poul Henning Jensen and Hjalte Gram

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