Unravelling the pathophysiological role of alpha-synuclein aggregation, transmission and neuroinflammation in neurodegeneration (Unravelling the pathophysiological role of alpha-synuclein aggregation, transmission and neuroinflammation in neurodegeneration (SYNaction)

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Misfolded protein aggregates are a common feature of several ageing-related neurodegenerative diseases. The discovery of the prion-like transmissible nature of amyloidogenic proteins suggests a pathogenic trigger which might propagate throughout the nervous system driving the progression of the disease. The molecular hallmark of synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are α-synuclein(αSYN)-rich deposits suggestive of one molecular event causing distinct disease phenotypes. We hypothesized that distinct phenotypes in synucleinopathies might correlate to heterogeneity in αSYN strains in patients. We also postulated that neuroinflammatory processes are linked to αSYN transmission and neurotoxicity.
αSYN assemblies were purified and amplified from human brain samples of PD, MSA and Dementia with Lewy Bodies (DLB) patients using Protein Misfolding Cyclic Amplification assay. These assemblies have been evaluated in vitro and in vivo by the different partners. Readouts include behavioural, imaging, biochemical and histochemical analysis of αSYN assemblies, aggregation and propagation of the induced lesions in the rodent brain and affected areas. Also, the involvement of the innate and adaptive immune system has investigated in vitro and in vivo. We have found that distinct alpha-synuclein strains can be isolated from the brain of patients with different synucleinopathies and we could demonstrate that they induce a different neuropathological, neurodegenerative and immunological phenotype in preclinical models for Parkinson's disease. A better understanding of the role of intercellular transmission and neuroinflammation in αSYN-linked neurodegeneration will contribute to early diagnosis, prevention and the development of novel therapeutic strategies for synucleinopathies and other ageing-related disorders.