The role of alpha-synuclein misfolding in Parkinson’s disease.

https://neurodegenerationresearch.eu/survey/the-role-of-alpha-synuclein-misfolding-in-parkinsons-disease/

Name of Fellow

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Institution
Funder

Wellcome Trust

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Country

United Kingdom

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The role of alpha-synuclein misfolding in Parkinson's disease.

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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Research Abstract
Aim To determine how oligomerisation of alpha-synuclein induces neuronal toxicity in Parkinsons disease. Objective 1: Molecular characterization of oligomerisation The key

intermediate goals: (a) to apply biophysical methods (single molecule TCCD and single molecule FRET) to characterize and isolate the different alpha-synuclein species (monomers,oligomers,fibrils) generated during aggregation of fluophore labeled alpha-synuclein (b) to test the effect of alpha-synuclein mutations a nd alpha-synuclein phosphorylation on aggregation Objective 2: Investigation of pathogenesis of oligomerisation in disease models The key intermediate goals are: (a) to characterize a range of mammalian stem cell derived neuronal models expressing different levels of alpha-synuclein. (b) to test the effect of different alpha-synuclein species on uptake and intracellular aggregation in disease models. (c) to investigate the effect of different alpha-synuclein species on cellular processes in particular mitochondrial function, calcium signaling and cell death. (d) to study how endogenous alpha-synuclein may aggregate in neuronal models using recombinant nanobodies that specifically recognize different alpha-synuclein species. Objective 3: Validating targets for therapy Any compound proven to inhibit formation of the toxic species will be tested in cell models to confirm whether it also abrogates toxicity. This represents the translation from in vitro modelling to rational d isease modifying drug design in Parkinson’s disease.

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