# Activated microglia regulate neuronal secretion of a-synuclein by exophagy through activation of neuronal JNK stress kinase

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**Question**
**Principal Investigators**

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**Related**
**Institution**

University of Copenhagen

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**Country**

Denmark

**Title of project or programme**

Activated microglia regulate neuronal secretion of alpha-synuclein by exophagy through activation of neuronal JNK stress kinase

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**Research Abstract**

Parkinson disease (PD) is the most common of the so-called a-synucleinopathies characterized by the abnormal accumulation of the small protein a-synuclein (AS). Within the past couple of years exciting new discoveries have caused a paradigm shift in the field: it is now suspected

that PD propagates in the brain through a ‘prion-like’ mechanism involving the transmission of pathological AS species between nerve cells. However, this theory is largely based on phenomenological evidence from animal models (or engrafted PD patients): no or only sparse mechanistic insight into the actual cellular processes responsible for nerve cell secretion (and uptake) of AS species have been gained. Neither does the theory account for the role of activated microglia, otherwise known to be essential for disease development. Based on previous findings from the Vilhardt lab, which have proposed a novel autophagy-based mechanism for secretion of AS from neurons, I have data suggesting that microglia cells might play a prominent role in PD propagation by modulating autophagy and AS secretion from neurons likely involving transcellular regulation of neuronal JNK activation. In the laboratory, I will test this hypothesis by a series of controlled experiments involving advanced molecular and cellular biology and microscopical imaging on diseased nerve cells. I will use immune cells and differentiated nerve cells derived from healthy human individuals and PD patients to assess the relevance of our findings in humans. If the hypothesis holds true, it could change the way we think about treating patients in the future, and importantly how to develop new and safe treatments.

**Further information available at:**

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