JPND research
EU Joint Programme – Neurodegenerative Disease Research

PrPC&PDK1

The PrP^{C} / PDK1 / TACE signaling axis at the cross-road of several aggregate-prone protein-associated neurodegenerative diseases

Neurodegenerative diseases such as Alzheimer's, Prion, Parkinson's diseases, Amyotrophic Lateral Sclerosis, Spino-cerebellar Ataxia and Fronto-temporal Dementia make up a group of pathologies with distinct etiologies and pathophysiological features characterized by the accumulation in the nervous system of abnormal proteins that are toxic for neurons. Although each disease displays specific clinical manifestations, the abnormal proteins may exert their toxicity through common pathways.

This project is based on our previous identification of neurodegenerative mechanisms common to both Prion and Alzheimer's diseases. In diseased neurons, an enzyme, PDK1, is over-activated and blocks the protective action of another enzyme, TACE, which not only amplifies the production of pathogenic prions (prion diseases) or neurotoxic Abeta peptides (Alzheimer's disease) but also renders diseased neurons highly sensitive to inflammatory factors. Inhibiting PDK1 in mouse models with prion or Alzheimer's diseases counteracts the toxicity of prions and Abeta and mitigates these pathologies.

Combining in vitro and in vivo approaches as well as the analyses of human cells and tissues, this project will probe the implication of the PDK1/TACE pathway in the above-mentioned neurodegenerative diseases. Currently, there are no efficient therapies to delay or stop these fatal diseases. Our work will determine if PDK1 is a therapeutic target for these disorders.

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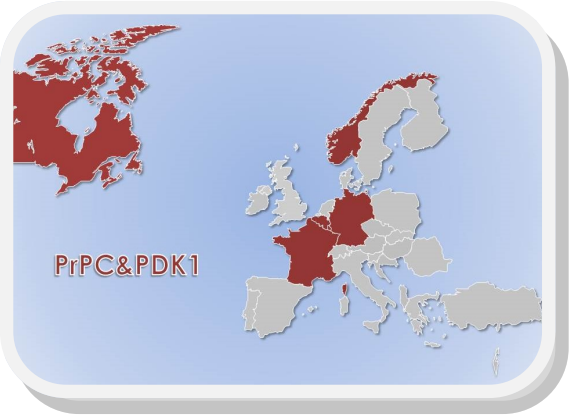

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* Contributions from participating JPND Member Countries are currently being finalised for this project