NIPARK

Targeting neuromelanin-linked neuronal dysfunction and degeneration in ageing and Parkinson's dis-ease using a combined imaging and brain stimulation approach

In Parkinson's disease (PD) there is a preferential degeneration of neurons containing the dark-brown cytoplasmic pigment neuromelanin (NM), including dopaminergic neurons of the substantia nigra and noradrenergic neurons of the locus coeruleus, the loss of which leads to characteristic motor and non-motor symptoms of the disease. However, the potential contribution of NM to PD pathogenesis has remained largely unknown because, in contrast to humans, NM does not appear spontaneously in most animal species, including rodents.

To overcome this major limitation, we recently developed the first experimental rodent model exhibiting age-dependent production of NM within PD-vulnerable neurons. This has revealed that intracellular NM accumulation above a pathogenic threshold can trigger neurodegeneration which replicates many features of PD. By taking advantage of this newly developed NM-producing rodent model, here we will combine the multidisciplinary expertise of the different partners to: (1) apply NM-sensitive imaging technologies, including MRI and PET, to detect the pathogenic NM threshold at a prodromal stage, in both rodents and humans, for the assessment of PD risk; (2) use different region-specific stimulation technologies, including transcranial focused ultrasound and optogenetic stimulation, to maintain NM levels below the identified pathogenic threshold and to reactivate dysfunctional NM-containing neurons prior degeneration. If successful, the results from this proposal could be envisaged for the screening of the general aging population to identify individuals at risk of developing PD (i.e., those approaching or reaching the pathogenic threshold of NM accumulation) and allow the prompt application of NM modulatory therapies in these subjects to prevent disease.

Total Funding : 0.74 M€

Duration : 3 years

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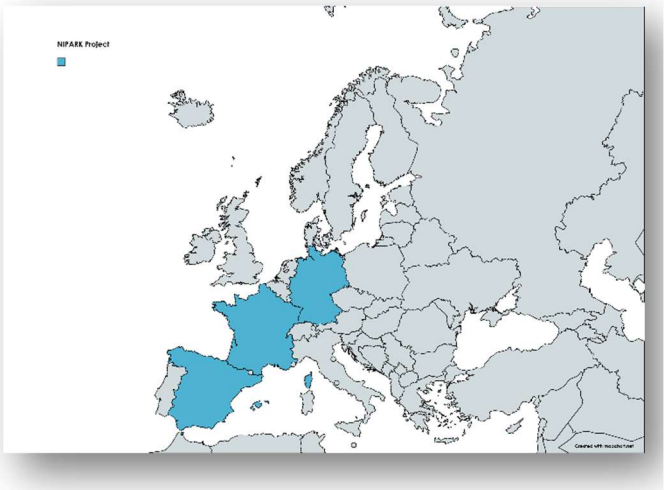

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