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Protocol for "Neuromelanin accumulation drives endogenous synuclienopathy in non-human primates"

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DISCLAIMER

The authors report no competing interests

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ABSTRACT

This study was aimed to develop and characterize
a non-human primate (NHP) model of Parkinson's disease mimicking the known neuropathological hallmarks of Parkinson's disease to the best possible extent. Accordingly, we sought to determine whether AAV-mediated enhanced expression of
human tyrosinase (hTyr) in the substantia nigra (SNpc) of non-human primates (NHPs) is able to induce a time-dependent accumulation of neuromelanin (NMel) in dopaminergic neurons, further triggering and endogenous synucleinopathy, progressive cell death and a pro-inflammatory scenario, in keeping with what was formerly reported in rats by taking advantage of a similar strategy (Carballo-Carbajal
et al., 2019). Furthermore, the potential prionoid spread of endogenous alpha-synuclein (a-Syn) species towards the
prefrontal cortex was analyzed, in an attempt to evaluate to what extent there is a propagation of endogenous a-Syn
by permissive trans-synaptic templating (e.g. the so-called Braak hypothesis). Adult juvenile NHPs (*Macaca fascicularis*)
were injected with adeno-associated viral vectors (AAVs) encoding either the hTyr gene (AAV-hTyr; delivered into the left SNpc) or a null construct for control purposes (AAV-null; injected into the right SNpc). In order to delineate a timeline for the underlying processes, one group of NHPs was sacrificed four months post-AAV deliveries (animals M308F4 and M310M4), whereby
the follow-up timing for second experimental group was settled at eight months post-AAVs surgeries (animals M307F8 and M309M8). Neuroimage studies (MRI and MicroPET) were conducted *in vivo* at
different time points. Upon animal sacrifices, brain tissue samples were processed for histological analysis comprising intracellular NMel levels, intracellular aggregates, nigrostriatal degeneration and neuroinflammation.

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