Current advances in gene therapy for parkinson's diease

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SUMMARY

Parkinson's disease (PD) is a neurodegenerative disorder characterized by severe motor symptoms (including resting tremor, cogwheel rigidity and bradykinesia) caused by the progressive loss of the dopaminergic nigrostriatal projection neurones by apoptosis (1). This leads to gradual depletion of the neurotransmitter dopamine from the striatum and consequent imbalance between the striatopallidal and striatonigral (basal ganglia) output pathways controlling movement (2). The main treatment for PD in its early stages is to provide dopamine via oral uptake of L-3, 4-dihydroxyphenylalanine (L-Dopa). However, chronic administration of L-Dopa eventually leads to loss of drug efficacy (*wearing off*) and the onset of disabling dyskinesias and motor fluctuations (*on-off*) (2).

We have used an equine infectious anemia virus (EIAV) vector (ProSavin®) to express three dopamine biosynthetic enzymes, namely tyrosine hydroxylase, aromatic L-amino acid decarboxylase, and GTP cyclohydrolase-1, essential for metabolising tyrosine to dopamine. This vector mediates dopamine production *in vitro* and *in vivo* and was previously demonstrated to correct the 6-OHDA lesion rat model of PD after stereotactic delivery to the striatum (3). We have further improved the vector and evaluated its therapeutic potential in a bilateral non-human primate (NHP) model of PD. ProSavin® was injected bilaterally into the striatum of MPTP-lesioned macaques using MRI-guided stereotactic surgery, and resulted in an increase in striatal dopamine and significant long-term reversal of motor deficits compared to control MPTP animals. Furthermore, gene transfer normalised internal globus pallidus activity and subthalamic nucleus metabolism, indicating restoration of normal basal ganglia functioning. L-Dopa administration to ProSavin® treated macaques led to increased levels of striatal dopamine but did not result in any runaway dyskinesias (4). This study has led to the initiation of a Phase I/II dose escalation-safety/efficacy clinical trial in France aiming at assessing the utility of this approach in treating late stage Parkinson's disease patients. This study will be discussed in relation to other gene therapy approaches also in clinical trials for PD.

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