GENE AND CELL THERAPIES FOR PARKINSON’S DISEASE - WHERE IS IT ALL GOING?
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Parkinson’s disease (PD) is a common neurodegenerative disorder of the CNS that is characterised pathologically by the presence of alpha-synuclein positive Lewy bodies at a number of different CNS sites. This pathology leads to a constellation of motor and non motor features, some of which are responsive to dopaminergic replacement therapy given that the classical biochemical deficit is the loss of the dopaminergic nigrostriatal pathway. This core event has led to a host of cell and gene therapy approaches that have sought to either:

(a) Replace the lost dopaminergic innervation to the striatum using dopaminergic cell transplantation (e.g. fetal ventral mesencephalic transplants);
(b) Restore or maintain the dopaminergic innervation to the striatum using neurotrophic factors (e.g. Neurturin gene therapy);
(c) Enhance the delivery of the dopamine within the striatum using synthetic enzymes for this neurotransmitter (e.g. ProSavin ®; AADC gene therapy approaches);
(d) Modulate the circuitry of the basal ganglia by changing some of the phenotypic properties of the cells within them (e.g GAD gene therapy).

These approaches have produced mixed results, but with enough encouraging data to try and take some of these therapies further in the clinic, especially given the advances that have been made in the genesis of dopaminergic neurons from stem cell sources. This latter approach has focussed on not just ES cells, but the use of induced pluripotent stem cells (iPSCs) and induced neuronal (iN) cells. However in order for these therapies to be effective, more thought has to be given to:

(a) The type of patient who is likely to maximally benefit from the novel treatment;
(b) The optimal stage of disease to deliver that therapeutic;
(c) The optimal dose and site;
(d) The long tern safety of the agent being delivered given the procedure is irreversible;
(e) The optimal trial design by which to assess that therapeutic given the limitations in terms of small patient groups.

In this talk I will explore all of this and sketch out the future therapeutic landscape using cell and gene therapies for PD, and what will need to be demonstrated with these therapies for them to be truly effective and competitive.

REFERENCES: