Nature Reviews Neurology **9**, 60 (2013); published online 8 January 2013; doi:10.1038/nrneurol.2012.266

PARKINSON DISEASE

Overcoming hurdles to stem-cell transplantation for treatment of Parkinson disease

Transplantation of stem cells to replace degenerating dopaminergic neurons is an attractive therapeutic option for Parkinson disease (PD), but has so far had limited success in patients. A recent study in macaques has suggested a novel approach to this strategy that has potential to improve therapeutic outcomes.

> “...DAT1 expression remained above baseline in treated monkeys for over 7 months...”

“Early transplantation trials in PD used foetal midbrain tissue containing dopaminergic neurons as a cell source, but postgraft functionality and safety of the foetal cells are a source of concern,” says Mari Dezawa, who led the new study. “Moreover, limited availability of foetal stem cells and related ethical considerations pose restrictions to [their] practical use,” she adds.

To address these issues, the researchers began by isolating mesenchymal stem cells (MSCs) from the bone marrow of five parkinsonian macaques. The cells were differentiated into dopamine-containing neurons *in vitro* through transfection of a plasmid that contained the intracellular domain of Notch 1, followed by cytokine stimulation. Immunohistochemical analysis revealed that the differentiated cells expressed markers of A9 dopaminergic neurons —the neuronal subtype that is most severely damaged in PD.

Next, Dezawa *et al.* transplanted the differentiated cells into the striatum of the donor monkeys. Such autologous transplantation obviates the need for immunosuppressive therapy, making this approach attractive for clinical translation.

Compared with sham-operated macaques, treated macaques exhibited modestly improved motor behaviours, such as performance in the hand-reach task, at 4 months and 8 months. In addition, PET scanning using ^{11}C-CFT, which specifically labels the dopamine transporter DAT1, showed increased DAT1 expression in the striatum of cell-engrafted versus sham-treated monkeys.

Importantly, DAT1 expression remained above baseline in treated monkeys for over 7 months, suggesting that some of the transplanted cells survived and integrated with striatal tissue. In previous studies, by contrast, undifferentiated MSCs did not show long-term survival following transplantation into rodents. “Future clinical applications towards a treatment for PD using MSCs with high efficiency are expected from this research,” says Dezawa.

Katie Kingwell

Original article Hayashi, T. *et al.* Autologous mesenchymal stem cell-derived dopaminergic neurons function in parkinsonian macaques. *J. Clin. Invest.* doi:10.1172/JCI62516

© 2013 Macmillan Publishers Limited. All rights reserved