In Translation

From Skin to Brain: A Parkinson’s Disease Patient Transplanted with His Own Cells

Malin Parmar1,2 and Anders Björklund1,2
1Developmental and Regenerative Neurobiology, Department of Experimental Medical Science, Wallenberg Neuroscience Center, Lund University, 22184 Lund, Sweden
2Correspondence: malin.parmar@med.lu.se (M.P.), anders.bjorklund@med.lu.se (A.B.)
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In a pioneering study in New England Journal of Medicine, Schweitzer et al. (2020) report on a patient with Parkinson’s disease who received a graft of dopamine neurons obtained from in vitro differentiated induced pluripotent stem cells, derived from the patient’s own skin fibroblasts, showing the feasibility of autologous transplantation for dopamine cell replacement.

Parkinson’s disease (PD) is a neurodegenerative disorder that primarily affects the dopamine (DA) neurons in the midbrain early in the disease process. The loss of DA neurons leads to lower levels of DA in the striatum, and as a consequence, the characteristic motor symptoms of bradykinesia, rigidity, and tremor result. There is currently no cure for PD, but treatments based on normalizing DA neurotransmission via medication are used to relieve the motor symptoms and maintain quality of life. While these can work well for many years, their efficacy declines over time, often associated with the emergence of side effects (Stocchi et al., 2008). Cell replacement therapies have long been an attractive prospect for the restoration of motor function in PD patients. Initial efforts using fetal DA neurons provided proof of principle that this approach can work (reviewed in Barker et al., 2015). However, the logistic and ethical problems associated with the use of tissue obtained from aborted fetuses, and the inability to standardize and quality control such material, prevents this approach from seeing wider use. Since their discovery, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) have been explored as alternative sources of cells for DA neuron replacement therapy. Both of these cell types can be used to derive authentic and functional DA neurons, and global efforts are ongoing to develop them for clinical use (Barker et al., 2017).

In a pioneering study published in New England Journal of Medicine (NEJM), Schweitzer et al. (2020) report the transplantation of autologous iPSC-derived DA progenitors in a patient with PD. This is the first report of a patient-specific cell-based therapy for PD and as such presents a major milestone in the field. The study was conducted under regulatory guidance from the US Food and Drug Administration (FDA) under Individual Patient Expanded Access, which is a potential pathway for a patient with an immediately life-threatening condition, or a serious disease or condition, to gain access to an investigational medical product for treatment outside of clinical trials (often referred to as compassionate use).

The patient was a 69-year-old man with a 10-year history of progressive idiopathic PD who reported poor control of his symptoms by the dopaminergic drug regimen. Pre- and post-transplant clinical assessments followed a routine similar to what has been used in the fetal cell trials (Barker and TRANSEURO Consortium, 2019). The patient was followed for 24 months after first surgery, and importantly, no adverse events related to intervention were reported and the patient did not decline in function during the course of the interventional observation. There was a modest (6%) decrease in levodopa equivalents as compared with doses used before the implantations. The change in putaminal 18F-DOPA uptake, as assessed by positron emission tomography (PET), was small but suggested the presence of a surviving graft. The imaging data are encouraging as they did not show any signs of tumor formation or transplant overgrowth, which is a main safety concern associated with the use of pluripotent stem cell-derived cell preparations. There were no signs of involuntary movements, dyskinesias, a graft-induced side effect that has been reported to occur in a significant fraction of patients receiving fetal cell grafts.

This report is published at a time when cell-based therapies for PD are at an exciting phase of development. The first (non-autologous) iPSC-based clinical trial was initiated at the Center for iPSC Cell Research and Application (CIRA) in Kyoto in 2018 where three patients have now been transplanted with DA neuron progenitors originating from the same iPSC line (http://www.cira.kyoto-u.ac.jp/en/faq/faq_patient.html), and a number of clinical trials using ESC- or iPSC-derived DA neurons are in a late phase of development (Barker et al., 2017). The Schweitzer et al. study is a case report of a single patient, receiving treatment under the US regulations for compassionate use. Although the road to an approved therapy will be long, this first case is a significant milestone as it shows the feasibility of the autologous cell therapy approach using the patient’s own cells.

The main attraction of autologous transplantation compared to standard allogenic pluripotent stem cell transplants is related to the fact that the autologous cells are immunologically identical to the recipient’s and can thus be used without the need of immunosuppression (Morizane et al., 2017). However, the generation of batches of clinical-grade iPSCs from each patient, and their differentiation into validated DA neuron progenitors, is challenging. As summarized by Jun Takahashi in a recent commentary (Takahashi, 2020), this process is laborious and
time-consuming, and the necessary quality checks of both the selected iPSC line and the final differentiated DA cell product from each line are quite complex. This team, led by Kwang-Soo Kim, used a variant of a commonly used so-called floor-plate protocol, based on dual smad inhibition and standard DA patterning factors (Kriks et al., 2011) combined with a novel monolayer spotting method to accommodate for scalability, and treatment with a chemical agent, quercitin, to remove potential pluripotent stem cells from the transplanted product. Very much to their credit, they published earlier this year a detailed and well-documented account of the iPSC derivation and differentiation procedure, as well as a report of the preclinical validation of the cells, using the same process that was used for the product delivered to the patient (Song et al., 2020). To make the preclinical assessments publicly available is of utmost importance for the field as it ensures transparency and provides the scientific community with the ability to scrutinize the data. Moreover, open access to the full dataset provides an important opportunity to retrospectively correlate clinical findings with the composition and phenotypic characteristics of the cell product, as well as information on the tools used to validate its safety and efficacy. If corresponding data are made available from all clinical trials in the field, this will help to form an understanding of
what criteria and tests best predict safety and efficacy when used in patients. To this end a global network, GForce-PD (http://www.gforce-pd.com/), has been created with the goal to share data between centers, learn from each other, and assist in the development and further improvement of the cell products and their delivery to the patients. The authors of this In Translation piece and the lead author of the current NEJM study under discussion belong to this network.

How do autologous transplants compare with approaches using cells derived from established and banked ESC or iPSC lines? As summarized in Figure 1, both approaches can be used to generate transplantable DA neuron precursors using similar differentiation strategies. A main disadvantage of the autologous approach is the need to derive new iPSCs for each patient, and the unavoidable variation from cell line to cell line and from each round of differentiation. As DA neuron precursors for transplantation are generated on demand, the batches used for safety and efficacy testing would be different from those that are transplanted (Figure 1A). In the allogenic approach, by contrast, the DA neuron precursors can be generated in large batches that can be thoroughly tested before being used in a large number of patients (Figure 1B), albeit with the need for immunosuppression extending over about a year. In the current study the patient received transplants in two surgery sessions staged 6 months apart, and two separately generated batches of DA progenitors were therefore used. This type of approach, therefore, is likely to yield variations in outcome, similar to what has been problematic in the fetal cell transplant trials, a problem that needs to be addressed more carefully as the field moves on. Nevertheless, this pioneering study points to the feasibility of future therapies based on the use of the patient’s own cells, a promising start that will stimulate further efforts along these lines.

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DECLARATION OF INTERESTS

M.P. is the owner of Parnar Cells AB and co-inventor of the US patent application 15/093,927 owned by Bioralint AB, 16/610,787 owned by New York Stem Cell Foundation, and EP17181588 owned by Millenyl Biotec. M.P. receives research funding from Novo Nordisk.

REFERENCES


