

Editorial

Repairing the Parkinsonian Brain

Anders Björklund^{a,*}, Bastiaan R. Bloem^b, Patrik Brundin^c and Howard Federoff^d

^aWallenberg Neuroscience Center, Lund University, Sweden

^bRadboud University Nijmegen Medical Center, Donders Institute for Brain, Cognition and Behavior, Department of Neurology

^cLaboratory of Translational Parkinson's Disease Research, Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, MI, USA

^dHenry and Susan Samueli College of Health Sciences, University of California, Irvine CA, USA

Keywords: Parkinson's disease, movement disorders, advanced therapies, gene therapy, cell therapy, growth factors

Cell and gene therapy for brain diseases have been long in the making. Starting with the first speculative ideas [1–3] and the initial exploratory trials in the 1980s and 90s [4, 5], followed by the major set-backs in the cell- and gene therapy fields at the turn of the century [6, 7], and the renewed developments seen during the last decade [8, 9]. This revival of the cell- and gene-therapy field has been driven by the remarkable technical developments that have given us access to increasingly more powerful molecular and genetic tools and techniques, and opened up for more refined approaches to therapy for neurodegenerative diseases, and Parkinson's Disease (PD), in particular.

In this Special Issue of Journal of Parkinson's Disease, *Repairing the Parkinsonian Brain*, we highlight some of the current strategies that are pursued with the goal to restore lost function and replace what is lost in the PD brain, with a special emphasis on the challenges, regulatory and ethical, that are associated with the translation of advanced therapeutic approaches into pioneering clinical trials.

In contrast to current medical treatments for PD patients, which are essentially only alleviating the

symptoms, the cell- and gene-based strategies pursued today offer the possibility to interfere with the underlying disease processes – thereby aiming to slow down the neurodegenerative process – and even to restore what is lost to the disease. Although the degenerative changes in PD are widespread, current treatment efforts – as covered in this Special Issue – are focused on the loss of midbrain dopamine (DA) neurons. This focus is well justified given that the degeneration of midbrain DA neurons is at the core of the disease process and the cause of many of the disabling motor impairments. Blocking DA neuron degeneration and restoring DA function back to normal is thus an essential component of any future restorative therapy. At the same time, we acknowledge that any approach that selectively tackles only the midbrain DA neurons will never be a panacea for all the problems experienced by persons living with PD. Much of the quality of life in later disease phases is caused by a wide range of nonmotor problems, which appear to be primarily related to pathology extending beyond the midbrain DA neurons. This recognition explains why we are beginning to see a “new phenotype” in persons who have received deep brain stimulation, which is also a powerful way of restoring dysfunction in the dopaminergic system – with prolonged follow-up, the motor improvements can continue to be gratifying, but such patients are

*Correspondence to: Anders Björklund, Wallenberg Neuroscience Center, BMCA11, 22184, Lund, Sweden. Tel.: +46 703146761; E-mail: anders.bjorklund@med.lu.se.

increasingly plagued by progressive nonmotor disability for which the deep brain stimulation is not an answer. So developments should ultimately also focus on neurorestoration of extranigral pathways.

The gene therapy approaches pursued so far are being developed along three parallel lines: delivery of neurotrophic factors, glial cell-derived neurotrophic factor (GDNF) and Neurturin, for DA neuron protection; delivery of DA synthetic enzymes for recovery of DA production in the DA-depleted striatum; and delivery of the glutamic acid decarboxylase (GAD) enzyme to the subthalamic nucleus for resetting of basal ganglia network activity [see Ref. 8, for review]. Critical to the progress of this field was the introduction of lenti- and adeno-associated virus (AAV) vectors for efficient targeted gene delivery to the brain. Using these gene delivery tools a number of explorative clinical trials have been performed over the last decade, some of which are still ongoing. Although the results obtained in these trials are mixed, the striking clinical improvements observed in some of the treated patients encourage further efforts along these lines.

In the chapters included in Part II of this issue we review the progress made in the trials using putaminal delivery of DA synthesising enzymes and highlight ongoing efforts to develop gene therapy approaches targeting two critical pathogenic mechanisms, alpha-synuclein aggregation and spread, and impaired lysosomal function. Adding to this, we include in Part III reviews that provide perspectives for new innovative developments in the delivery of genes and growth factors to the PD brain, and endoplasmic reticulum (ER) stress as a target for disease modifying therapies, the CDFN/MANF family of neuroprotective factors in particular.

The cell therapy approach seeks to replace the lost midbrain DA neurons and restore dopaminergic neurotransmission in the DA-denervated striatum. The development in this field goes back to the early exploratory trials using fetal human midbrain tissue that were performed in the 1980s and 90s. Despite encouraging results in some of the grafted patients, the approach using fetal cell transplant was largely abandoned due to the negative outcome of two NIH-sponsored placebo-controlled clinical trials published in 2001 and 2003 [see Ref 9, for review].

This field has seen a dramatic revival during the last decades thanks to major developments in the stem cell field and novel insights into the genetic mechanisms underlying midbrain DA neuron development. The discovery of the human embryonic stem

cell (hESC) in 1998, and the invention of the cellular re-programming technique for generation of induced pluripotent stem cells (iPSCs) in 2004, were major milestones in this development, and the development of the so-called floor-plate protocols for generation of authentic midbrain DA neurons from hESCs and hiPSCs in 2011-2012, set the stage for the rapid progress we have witnessed during the last decade.

Major players from both biotech and pharma have entered the field, and based on refined protocols for efficient production and up-scaling of GMP certified batches of transplantable human midbrain DA neuron precursors, the first stem cell-based clinical trials for DA cell replacement in PD are now underway [9]. In two reviews, in Part II of this issue, we highlight two lines of research aimed to promote further development of the cell therapy approach: (a) the pre-clinical studies aiming to optimise the composition of the graft cell preparation and to achieve more complete anatomical and functional integration of the grafted DA neurons, akin to more complete circuitry repair; and (b) the efforts being made to design or engineer the grafted cells to evade the immune system in order to reduce or eliminate the need of immunosuppressive treatment of the patients, thus paving the way for the next generation of improved grafting protocols. Although the cell- and gene-based approaches so far have developed independently and in parallel, their combination may offer interesting possibilities. Indeed, the full impact of DA neuron replacement therapy may be achieved in combination with a neuroprotective or disease modifying gene-based intervention – the grafted cells replacing the lost DA neurons and the genes blocking further progression of the disease, and keeping the graft from possibly being ‘attacked’ by the underlying neurodegenerative process itself.

The cell and gene therapy field is in an exciting stage of development and we can expect to see a wide spectrum of innovative ideas tested in exploratory clinical trials in the coming years. Intracerebral delivery of cells or genes, however, is a form of advanced therapy that is irreversible and that requires neurosurgical intervention. Pioneering trials in this field face regulatory and ethical challenges that are radically different from those applied to conventional drug trials. Such invasive procedures will have to be compared against a matched placebo intervention, particularly in a condition like PD where the placebo response can be pronounced and prolonged. The design of such placebo-controlled surgical trials require careful consideration. In the first four reviews,

in Part I of this issue, we provide different and complementary perspectives on the complex regulatory requirements and the design and initiation of first-in-man trials, as well as the patient's perspective on the concerns and worries related to the participation as a subject in demanding trials that extend over long time, and where the outcome and risks are uncertain. Small exploratory trials are essential steps along the way, but they have to be carried out with great care, and early patient involvement in the planning and initiation of such trials is imperative. The risks have to be minimised and weighed against the potential benefits of the enrolled patients, realising that the approach will need to be adjusted and improved in a step wise manner to ensure effective delivery of the cell and gene product and optimise the outcome. But it will be well worth the effort: the next breakthrough in the treatment of PD will be based on interventions that block disease progression and restore function back to normal. In this perspective these novel treatment modalities hold great promise.

DISCLOSURES

None of the authors has any relevant disclosures to make.

REFERENCES

- [1] Brundin P, Strecker RE, Clarke DJ, Widner H, Nilsson OG, Astedt B, Lindvall O, Björklund A (1988) Can human fetal dopamine neuron grafts provide a therapy for Parkinson's disease? *Prog Brain Res* **78**, 441-448.
- [2] Horellou P, Marlier L, Privat A, Mallet J (1990) Behavioural Effect of Engineered Cells that Synthesize L-dopa or Dopamine after Grafting into the Rat Neostriatum. *Eur J Neurosci* **2**, 116-119.
- [3] Kaplitt MG, Leone P, Samulski RJ, Xiao X, Pfaff DW, O'Malley KL, During MJ (1994) Long-term gene expression and phenotypic correction using adeno-associated virus vectors in the mammalian brain. *Nat Genet* **8**, 148-154.
- [4] Lindvall O, Brundin P, Widner H, Rehnström S, Gustavii B, Frackowiak R, Leenders KL, Sawle G, Rothwell JC, Marsden CD, Björklund A (1990) Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. *Science* **247**, 574-577.
- [5] Freed CR, Breeze RE, Rosenberg NL, Schneck SA, Kriek E, Qi JX, Lone T, Zhang YB, Snyder JA, Wells TH, Olson Ramig, Thompson L, Mazziotta JC, Huang SC, Grafton ST, Brooks D, Sawle G, Schroter G, Ansari AA (1992) Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease. *N Engl J Med* **327**, 1549-1555.
- [6] Smaglik P (2000) Clinical trials end at gene-therapy institute. *Nature* **405**, 497.
- [7] Check E (2003) Parkinson's transplant therapy faces setback. *Nature* **424**, 987.
- [8] Axelsen TM, Woldbye DP (2018) Gene Therapy for Parkinson's Disease, An Update. *J Parkinsons Dis* **8**, 195-215.
- [9] Barker RA, Parmar M, Studer L, Takahashi J (2017) Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era. *Cell Stem Cell* **21**, 569-573.