

Review

Bringing Advanced Therapies for Parkinson's Disease to the Clinic: The Scientist's Perspective

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Abstract. After many years of preclinical development, cell and gene therapies have advanced from research tools in the lab to clinical-grade products for patients, and today they constitute more than a quarter of all new Phase I clinical trials for Parkinson's disease. Whereas efficacy has been convincingly proven for many of these products in preclinical models, the field is now entering a new phase where the functionality and safety of these products will need to stand the test in clinical trials. If successful, these new products can have the potential to provide patients with a one-time administered treatment which may alleviate them from daily symptomatic dopaminergic medication.

Keywords: ATMP, clinical trial, dopaminergic neurons, regenerative therapy, stem cells, transplantation

INTRODUCTION: WHY DO WE NEED ADVANCED REGENERATIVE THERAPIES FOR PARKINSON'S DISEASE?

Ever since the discovery of Parkinson's disease (PD) in the early 19th century, there has been intense focus on trying to identify the underlying cause of the disease as well as the mechanism of disease progression. However, while the development of early symptomatic treatments for the disease has been successful, we have yet to develop disease-modifying

treatments to halt or slow progression of PD. Despite promising data from animal models, not a single disease-modifying therapy for PD has until now passed through Phase III clinical trial with positive outcome. Recently, there has been much anticipation to antibody therapies which can block propagation of α -Synuclein (α -Syn) pathology in the brain. However, in April 2020 Prothena/Roche announced that their therapy Prasinumab had failed to meet the primary endpoint of reduction on the Unified Parkinson's Disease rating scale (UPDRS) [1]. More phase II trial results are expected this year to uncover the clinical efficacy of α -Syn antibody technologies. The depressing conclusions so far likely reflect the fact that we still do not understand what triggers PD at its infancy, or why patients display such variable patterns of spread of pathology throughout the

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brain. Furthermore, the pathogenesis of PD is highly complex, involving damaging effects due to protein aggregation, inflammation, mitochondrial dysfunction, impaired autophagy and reactive oxygen species just to mention a few [2], and it may be naive to think that a single molecule can halt this multitude of deleterious processes. It is thought-provoking that the drugs which are currently showing most promising disease-slowing effects in clinical trials are GLP-1 agonists, which have an unclear mechanism of action proposed to involve modulation of several cell types including neurons, glia and immune cells [3, 4]. While refined and efficacious disease-modifying treatments are still struggling to reach the market, patients are in dire need of therapies which provide better quality of life and which are effective beyond the initial period after diagnosis. Compared to symptomatic dopamine (DA)-modifying medications, gene and cell therapies have the potential to provide more refined solutions to a complex problem by restoring neuronal signaling and in some cases even circuits in the diseased brain. As such, cell therapies such as DA cell replacement have the potential to significantly minimise the need for DA medications, relieving the patients not only of primary motor symptoms, but also of the severe side effects accompanying the ever-increasing doses of medication required to keep the progressing disease in check.

ADVANCED THERAPIES FOR PARKINSON'S DISEASE PASSING THROUGH THE PIPELINE

Until now, only few advanced therapeutic medicinal products (ATMPs) have been tested beyond initial Phase I/II clinical trials for PD. Overall, trials involving delivery of neurotrophic factors for supporting DA neuron survival, i.e., AAV-Neurturin (CERE-120) and GDNF infusion have shown disappointing outcomes on efficacy parameters [5, 6]. This likely reflects the fact that damaged DA neurons are difficult to rescue from cell death when disease pathology is ongoing. A novel gene therapy trial relying on supplying GBA1 to GBA mutation carriers is currently in Phase-I clinical trial, and will provide important information on whether GBA mutations alone are central in driving the progression of the disease in already diagnosed patients [7]. Other gene therapies are based on strategies to alter neurotransmitter production, either through hijacking

non-DA neurons to produce DA by supplying key DA enzymes (ProSavin: *AADC*, *TH* and *CHI*) or by increasing inhibitory signals from the subthalamic nucleus (STN) through AAV-GAD expression. Both approaches have shown moderate efficacy on UPDRS scores in clinical trials and are being explored further in new trials [8, 9]. However, an initiated Phase-II gene therapy trial with AAV-AADC (VY-AADC02) was halted by the FDA in December 2020, and the future development of this product is currently uncertain [7, 10]. Evolving from these early efforts with ATMPs, more advanced products are being developed and cell and gene therapies now constitute 27% of all ongoing Phase I studies in PD (14 out of 51 trials by January 2020), thereby clearly marking a new era of advanced therapies moving in larger numbers from the lab into the clinic [7]. New on this stage is the emergence of DA cell replacement products based on pluripotent stem cells (PSCs), which have the potential to yield authentic and fully functional midbrain DA neurons, the type which is lost in PD.

CLINICAL TRANSLATION OF DA CELL REPLACEMENT THERAPIES: WHERE ARE WE NOW?

The concept of DA cell replacement therapy has a rich clinical history based on allografting of human fetal ventral mesencephalic tissue, with estimates of over 300 PD patients transplanted over the past 30 years [11]. Patient outcomes have been variable, with some patients able to reduce or discontinue medications for years while others suffered from graft-induced dyskinesias. Two double-blinded, placebo-controlled trials failed to meet their endpoint which led to a re-evaluation of fetal cell therapies for Parkinson's, eventually leading to the initiation of the EU-funded TRANSEURO trial using improved protocols for fetal tissue preparation and more rigorous patient selection [12]. This trial has recently completed transplantation of all 11 patients included in the trial with fetal tissue, and clinical results are expected during 2021/22 [12]. Along with earlier fetal cell work, results from this trial will provide an important framework for stem cell-based therapies to come.

Clinical trials using PSC-based therapies have only just begun (see summary in Table 1). The first PSC-based trial for PD (ISCO trial) was initiated in Australia in 2016, using parthenogenetic PSC-derived neural progenitor cells of a non-DA fate [13]. These cells are proposed to have a more

Table 1
Pluripotent stem cell products in the clinical trial pipeline for PD

Cell product	Site of development (Company/Institution)	Immune matching	MoA	Trial site	Preclin. data	Trial start	Patients included*	Clinical data trial ID
ISC-hpNSC (Human parthenogenetic hESC-derived NSCs)	International Stem Cell Corporation (ISCO)	Allogeneic, non-matched	Trophic support	Australia	[13, 38, 39]	2016	12	N/A NCT02452723
Human parthenogenetic hESC-derived ventral midbrain progenitors	Chinese Academy of Sciences, Beijing	Allogeneic, HLA matched and non-matched	DA-CRT	China	[40]	2017	(50)	N/A NCT03119636
hiPSC-derived ventral midbrain progenitors	Harvard University	Autologous	DA-CRT	USA	[41]	2017	1	[29] IND No. 17145
hiPSC-derived ventral midbrain progenitors	Kyoto University	Allogeneic, HLA matched and non-matched	DA-CRT	Japan	[17, 42, 43]	2018	(7)	N/A UMIN000033564
MSK-DA01 (hESC-derived ventral midbrain progenitors)	Weill Cornell/Memorial Sloan Kettering/ BlueRock Therapeutics	Allogeneic, non-matched	DA-CRT	USA	[16, 19, 20, 44]	2021	(10)	N/A NCT04802733
STEM-PD (hESC-derived ventral midbrain progenitors)	Lund University/ Cambridge University	Allogeneic, non-matched	DA-CRT	Sweden UK	[30, 45–50]	Est. 2022	(8)	N/A EudraCT 2021-001366-38

MoA, Mechanism of Action; NSC, Neural stem cell; DA-CRT, Dopamine cell replacement therapy; N/A, not available. *Patient numbers in brackets are total no. of planned patients in trials which are not yet completed. Patient numbers without brackets are completed, transplanted patients.

indirect mechanism of action, working potentially through trophic support. However, multiple groups have shown through genetic engineering in preclinical models that it is specifically the midbrain DA neurons which are responsible for reverting symptoms in animal models of PD [14–16].

Following this rationale, Jun Takahashi and colleagues launched the first PSC-based midbrain DA neuron cell replacement in Japan in 2018 using an allogeneic iPSC approach [17, 18]. Just recently, a collaborative effort between Weill Cornell, Memorial Sloan Kettering, and BlueRock Therapeutics was granted permission by the FDA to advance to Phase 1 clinical trial in the US with an hESC-based midbrain DA product (MSK-DA01) originally developed by Lorenz Studer [19–21]. This trial is anticipated to begin later this year. In an equivalent European effort, Malin Parmar and colleagues have provided strong proof of concept for their hESC-based product and are aiming to begin clinical trials in the EU in 2022. These groups working on PSC-based products have been meeting annually since 2014 in the research-based network GForce-PD with the aim of sharing experiences to bring the best treatments forward for the PD community. Building on these academically led advancements, three additional companies, Sumitomo Dainippon Pharma, FujiFilm Cellular Dynamics Inc. and Novo Nordisk have also announced the development of PSC-based cell products for treatment of PD.

The trials mentioned above are based on allogeneic cell transplantation strategies. Induced pluripotent stem cell technology could provide an autologous approach with the benefit of genetic matching at the cost of time, logistic complexity and potential variability. For intracerebral therapies, it is not clear that autologous approaches will be advantageous in the immunoprivileged brain since fetal cell allografts have demonstrated robust and long-lived survival up to 24 years without long term immune suppression [22–28]. Relying on autologous grafting could limit the accessibility of stem cell therapies due to the cost and the complication of batch-to-batch variation in differentiation efficacy. Nevertheless, one cannot discount the possibility that the immune response to grafted allogeneic cells can limit efficacy. A recent single patient case led by the group of Kwang-Soo Kim at Harvard demonstrated proof of concept for the autologous transplantation approach [29]. The Kim group, as well as the US-based company Aspen Neuroscience, is now pursuing further clinical trials using autologous iPSCs for transplantation.

LOOKING TOWARDS THE FUTURE OF PSC-BASED CELL THERAPIES

It has taken around twenty years of intensive preclinical work to produce clinically acceptable pluripotent stem cell-derived human DA neurons that function efficiently in PD animal models. While this is great progress, much remains to be learned from clinical trials to improve cell products further. Careful work by the Parmar lab [30] has shown equivalence between fetal cell and PSC-based dopamine neurons in animal models of PD, but clinical data will be crucial to assess this equivalence in patients. Another unresolved question is whether transplanted DA neurons are “self-regulating.” That is, DA neurons might receive feedback from the brain that naturally balances and limits dopamine release. This is important since excessive dopamine release might result in dyskinesias (involuntary movement) [31]. Understanding this biology in humans will inform our strategy for patient dosing.

Another factor affecting dose is the observation that many neurons die after transplantation. It is not known why this occurs, and excess cells must be transplanted to account for this loss and assure adequate dosing. The delivery device itself creates an injury and a localized immune reaction, and large numbers of dead cells could alert the immune system to the transplanted cells. Beyond just the transplantation period itself, monitoring immune reactivity in allogeneic and autologous cell transplantation trials will be key to understanding the role of the immune response to grafted cells and is crucial for future cell therapy development. A better understanding of the immune response to grafts is needed to evaluate whether allogeneic cell sources can survive and escape rejection longterm, or if the autologous cells will provide a clinical advantage despite the many hurdles associated with their manufacturing. Many groups are further looking into the possibilities of using gene-edited allogeneic cell sources which can escape immune recognition for future universal use in patients to avoid the complexities and cost of making a personalized medicine [32–35]. Such cell lines must however be used with caution since these cells might inadvertently function as host cells to amplify viruses or permit uncontrolled cell growth. As such, incorporation of “suicide genes” into such engineered cells would allow the clinical option to chemically ablate the grafted cells if required [36, 37].

One inconvenient truth learned from the fetal cell trials is that it can take several years after

transplantation to achieve optimal clinical function from cell replacement therapies. This makes the choice of a clinical endpoint critical to assure the strongest clinical signal and reduced chance for placebo effects. Another key piece to the puzzle remains the patients themselves. PD has been increasingly recognized as a syndrome with a range of clinical courses. Increasing knowledge of PD subtypes and results from stem cell trials will allow us to better understand which patients will truly benefit from cell replacement therapies.

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CONFLICT OF INTEREST

Mark Tomishima holds several patent agreements and is an employee of BlueRock Therapeutics, a company that plans to commercially develop the DA01 product. Agnete Kirkeby holds several patent agreements and is a consultant for Novo Nordisk A/S on the development of the STEM-PD product.

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