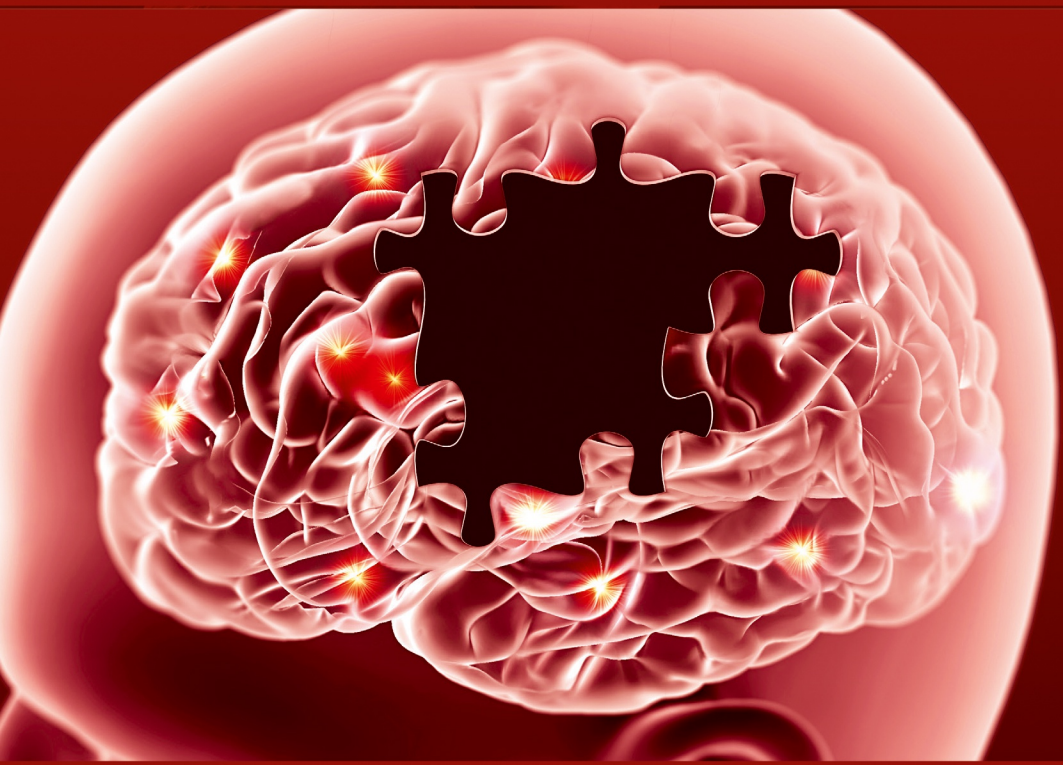
INTERNATIONAL REVIEW OF MOVEMENT DISORDERS

Device-Aided Therapies in Parkinson's Disease

Volume 7



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VOLUME SEVEN

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ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

First edition 2024

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ISBN: 978-0-443-31468-1
ISSN: 2666-7878

Publisher: Zoe Kruze
Acquisitions Editor: Mariana L. Kuhl
Editorial Project Manager: Sneha Apar
Production Project Manager: A. Maria Shalini
Cover Designer: Gopalakrishnan Venkatraman
Typeset by STRAIVE, India

CHAPTER TEN

The future: Stem cells? Current clinical trials using stem cells for dopaminergic cell replacement

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International Review of Movement Disorders, Volume 7
ISSN 2666-7878
https://doi.org/10.1016/bs.irmvd.2024.08.004

1. Introduction

Parkinson's disease (PD) is an age-related chronic, progressive neurologic disorder that currently has neither a cure nor a treatment to slow disease progression. It is the second most common neurodegenerative disorder after Alzheimers disease. According to the Global Burden of Disease study, neurological disorders are currently the leading source of disability around the world, and the fastest growing of these disorders is PD (in age-standardized rates of prevalence, disability, and deaths) (GBD 2016 Neurology Collaborators, 2019). Affecting approximately 1% of people >65 years, global estimates in 2019 reported over 8.5 million individuals with PD, a number projected to double and reach >12 million by 2040 (Dorsey, Sherer, Okun, & Bloem, 2018), with potential contributions from longer disease duration and environmental factors (GBD 2016 Neurology Collaborators, 2018).

The economic burden is enormous. For the US, the projected PD prevalence will be 1.6 million with an estimated economic burden surpassing 27 billion USD by 2037 (Yang et al., 2020). In Sweden, 22,000 individuals suffer from the disease resulting in an economic burden of EUR 247 million every year for Sweden only (Hjalte, Norlin, Kellerborg, & Odin, 2021). Approximately 10% of all PD patients are diagnosed at an age earlier than 50 years old and, for these patients, a disease course for more than 20 years is likely. In Japan, approximately 210,000 patients suffer from PD based on the prevalence (166.8 per 100,000 population, 2004) with an estimated economic burden of 427 billion yen (281 million USD). Those numbers have been increasing as the population has aged (Yamawaki, Kusumi, Kowa, & Nakashima, 2009).

Parkinson's disease leads to typical motor features such as resting tremor, bradykinesia, rigidity, and gait and balance disturbances as well as a number of non-motor features. Although disruptions in several distinct neurotransmitter systems give rise to those symptoms and signs, the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) underlies the majority of motor symptoms (Bloem, Okun, & Klein, 2021). It is this progressive loss of dopamine (DA) input to striatal medium spiny neurons that results in dysregulation of complex downstream circuits responsible for modulating motor function.

By the time of clinical diagnosis, there is some loss of control of motor functions and a substantial percentage of SNpc DA neurons are already lost.

Current oral treatments for PD mainly rely on alleviating motor symptoms by drugs aiming at replacement of DA (L-Dopa, DA agonists and enzyme inhibitors slowing the breakdown of DA), although drugs affecting other neurotransmitter systems such as anticholinergic agents may also be used. These may then be combined with pharmacological therapies addressing the non-motor symptoms.

Pharmacological treatments are initially highly effective during the early stage of the disease, but due to the systemic administration, DA is delivered in a non-physiologic spatial and temporal pattern. Ultimately, treatments are limited by side effects. For example, the pulsatility of levodopa therapy, with non-physiological stimulation of DA receptors in the striatum, and its continued use results in complications that include end-of-dose wearing off and levodopa-induced dyskinesia (LID). Other common adverse effects resulting from off-target effects include sleepiness, hallucinations, delusions, impulse control disorders and other problems (Foltynie et al., 2024).

In individuals with PD for whom medications eventually provide insufficient relief, surgical approaches have the potential to pseudo-normalize the basal ganglia outputs that are disrupted in this disease and thus reduce key motor symptoms. These approaches include deep brain stimulation, to modulate activity of the dysregulated output nuclei of the basal ganglia and thereby improve motor function (Foltynie et al., 2024). Newer methods for non-incisional and precisely targeted lesions using magnetic resonance-guided focused ultrasound are approved in some countries for clinical use for PD (Verhagen Metman, Monje, Obeso, & Martinez-Fernandez, 2024).

Importantly, none of the currently available treatments exceeds a purely symptomatic effect or has the ability to repair or restore the DA circuit and thereby change the slope of disease progression (Armstrong & Okun, 2020). Thus, despite the existence of multiple diverse therapeutics for PD, there is an urgent clinical need to provide a more effective and long-term treatment, that will restore neuronal function to provide continuous relief of motor symptoms.

2. The concept and history of cell replacement in Parkinson's disease

Although PD is heterogeneous in its clinical presentation, pace of progression, genetic association, and even pathology, a unifying finding is that the characteristic motor symptoms and signs reflect the progressive loss of nigral DA neurons. This makes the concept of treating Parkinson's motor

symptoms using a restorative approach, providing physiologic or "pseudo-physiologic" striatal DA delivery, particularly compelling.

The notion to replace the progressively lost DA neurons with new, healthy DA producing cells in PD is an approach that has been tested experimentally and clinically for >45 years.

The concept is primarily based on three hypotheses:

1. The predominant motor symptoms of PD are dependent on the loss of one cell type: DA neurons in the nigrostriatal pathway
2. DA neurons grafted into the striatum (target region of DA release) can survive and functionally replace lost neurons
3. The chronic physiological delivery of DA to the striatum can treat DA-responsive motor aspects of PD

Ideally, the grafted cells would be able to integrate into the host circuit and release DA in a regulated fashion.

2.1 History

In 1979, the first preclinical data were published showing that fetal mesencephalic DA-rich tissue transplanted to the brain can ameliorate signs of experimental PD in rats (Bjorklund & Stenevi, 1979; Perlow et al., 1979), opening for the first time the possibility that PD may be treatable with transplants of healthy DA cells and providing a strong platform from which to launch first in human studies.

Historically, before the more recent advances in stem cell technology, early efforts to replace striatal DA inputs used a variety of cell sources. The first approaches to replace DA neurons in clinical trials used autologous DA-producing cells such as adrenal medulla cells, carotid body cells and sympathetic ganglionic tissue to provide a catecholaminergic source.

2.1.1 Autologous adrenal medulla cells

In the very first clinical trials, patients received adrenal medulla cells/tissue implanted into the striatum. However, despite ca. 50 patients receiving grafts with adrenal medulla tissue, this method did not provide any significant clinical benefit but caused adverse effects, and upon autopsy no surviving tissue could be found (Peterson, Price, & Small, 1989), so that no further development of this approach was pursued (Backlund et al., 1985; Lindvall et al., 1987; Madrazo et al., 1987; Wang et al., 2023).

2.1.2 Carotid body cells

The carotid body contains neural-crest-derived DA glomus cells that are similar to the chromaffin cells of the adrenal medulla. These cells release

DA in response to hypoxia and secrete glial cell line derived neurotrophic factor (GDNF), providing the rationale for their use in PD. A small number of patients was treated with this method and some functional improvement reported (Arjona et al., 2003; Minguez-Castellanos et al., 2007).

2.1.3 Sympathetic ganglion tissue

Another approach was to resect sympathetic ganglion tissue (containing DA and norepinephrine cells) and transplant this into striatum. Even though some reduced OFF time was reported, no further clinical trials were performed (Itakura et al., 1994; Itakura, Uematsu, Nakao, Nakai, & Nakai, 1997; Nakao et al., 2001; Nakao, Shintani-Mizushima, Kakishita, & Itakura, 2004).

2.1.4 Human retinal pigment epithelial cells

Spheramine comprises human retinal pigment epithelial (RPE) cells harvested at autopsy delivered on an excipient of cross-linked porcine gelatin microcarriers. It has been tested in clinical trials due to its potential to deliver levodopa. Based upon successful preclinical testing in rodent and non-human primate models, an open-label single-center clinical trial of unilateral cell transplant was conducted that demonstrated an average 48% improvement in the Unified Parkinsons Disease Rating Scale (UPDRS) motor "off" score at 12 months, and no serious adverse events related to the intervention (Bakay et al., 2004; Stover et al., 2005; Stover & Watts, 2008). A phase II, multi-center, randomized, sham surgery-controlled, double-blind clinical trial then failed to replicate the benefit, and with more deaths in the active arm vs sham surgery arm this program was not continued (Gross et al., 2011). Autopsy of one participant at 6 months pointed to poor cell survival of grafted cells (Farag, Vinters, & Bronstein, 2009).

Therefore, based upon these experiences, it became evident that cell replacement needs to replace the DA neurons of the SNpc by cells that are as authentic to A9 SNpc DA neurons as possible.

2.15 Fetal cells

In 1987, the first intrastriatal transplantations with human fetal ventral mesencephalic (hfVM) tissue were performed in PD patients (Lindvall et al., 1990, 1989). Since then, about 450 PD patients have been grafted with hfVM tissue in the striatum in a number of open-label trials and two double-blind, placebo-controlled trials. Even though the open-labeled trials repeatedly reported substantial and long-lasting clinical benefit of fetal DA cell transplants, the double-blind placebo controlled trials could not

demonstrate a clinical significant benefit (Freed et al., 2001; Olanow et al., 2003). Some of this failure has been attributed to the clinical study design such as choice of endpoints and outcome measures, tissue dosing and insufficient duration of immunosuppression. However, a meta-analysis of the clinical trials using fetal tissue shows that ca. 30% of patients do have a substantial and meaningful improvement in OFF motor scores (Barker, Barrett, Mason, & Bjorklund, 2013). Some individual patients have also demonstrated a long-term effect associated with normalization of DA on positron emission tomography (PET) imaging even making pharmacological treatment unnecessary (Kefalopoulou et al., 2014).

There is clear evidence that grafted fetal cells can survive for decades despite that the underlying PD pathology is ongoing and show robust fiber outgrowth and innervation of the host striatum by donor-derived DA neurons (Kordower, Chu, Hauser, Freeman, & Olanow, 2008; Li et al., 2008, 2016).

In some post-mortem studies of patients with PD transplanted with hfVM tissue, alpha-synuclein pathology (i.e., Lewy bodies) could be detected in hfVM-derived DA neurons. The observed pathology in the transplanted neurons progressed, however, with slow kinetics (ca. 2% of neurons affected at 12 years, 5% of neurons at 16 years and 12% of neurons at 24 years) and did not impact the function of the graft (Li et al., 2008; Li et al., 2010; Li et al., 2016).

Those previous clinical transplantation studies using fetal DA cells have paved the way for the use of other cells sources to replace A9 midbrain DA neurons. They have provided the proof of principle that grafted neurons can survive several decades in the host brain, integrate, release DA and lead to significant and long-lasting improvement of motor symptoms.

2.2 TRANSEURO: An optimized clinical trial design to test fetal DA neurons

The cumulative re-analysis of the previous open-label and double-blind, placebo controlled trials led to the design of an optimized clinical trial design for cell transplantation, called TRANSEURO (Clinicaltrials.gov; NCT01898390) across Europe transplanting fetal DA neurons (Barker et al., 2024). This new clinical trial set out to better define patient selection and evaluation; improve trial design; to standardize tissue dissection and preparation as well as tissue implantation in order to optimize clinical outcome. This trial was recently concluded (Barker et al., 2024; Barker & TRANSEURO consortium, 2019).

The TRANSEURO study had two major parts: (i) a longitudinal natural history study of early stage younger-onset PD patients, who have been identified as the optimal group for this type of restorative therapy; and (ii) an optimized cell replacement study in this patient cohort using hfVM tissue.

The trial design of the transplantation arm differed from previous trials using fetal cells in a number of points that had been identified as key factors correlating with good clinical outcomes in grafted patients (Barker et al., 2013); (see Box 1).

Between 2015 and 2018, transplantations of 11 patients (out of 20 planned) were completed in this trial. A large number of surgeries had to be canceled due to shortage of tissue for grafting, resulting in substantial delays, logistic complications and burdensome experiences for the patients.

Even though many lessons could be learned from grafting hfVM tissue, the previous trials show that this tissue cell source cannot be used as a globally available therapy due to those logistic issues and the lack of standardization of the cells and the procedure. In addition to its low availability, there are multiple other barriers to using fetal tissue as a cell source, thus highlighting the critical need for new sources of authentic and functional human mesencephalic DA neurons of high purity and consistent quality.

BOX 1 Key factors correlating with good clinical outcome in grafted patients

- transplantation of a sufficient numbers of DA cells
- ensuring sufficient immunosuppression for at least 1 year to avoid immune rejection of the grafted allografts
- minimizing serotonergic (5-HT) contamination of the cell product to reduce the risk of graft-induced dyskinesias (GIDs)
- ensuring the even distribution of the cells across the grafted striatum to avoid creating excessive DA densities ("hot spots") which have also been linked to GIDs
- electing younger-onset, less advanced PD patients without significant LIDs; and
- ensuring long-term follow-up of patients to allow time for the transplanted cells to become mature and functional

3. Stem cells for transplantation therapy

To ensure further progress and clinical translation of cell therapy for PD, new bankable cell sources had to be identified and developed according to clinical safety and efficacy criteria, and national and international regulations. Several stem cell sources have therefore been utilized to obtain transplantable DA progenitor cells, of which pluripotent stem cells have shown the greatest promise of success in producing authentic A9 neurons.

Human pluripotent stem cells (hPSCs) have the unique feature that they represent the earliest stages of development in the embryo, and thereby they host the unique potential to generate all cells of the human body. Pluripotent stem cells can be derived from the inner cell mass of the early blastocyst, which is an embryonic structure forming at around 5–7 days after fertilization of the oocyte. Such blastocysts can be retrieved from surplus embryos generated at in vitro fertilization clinics. Pluripotent stem cells derived from the blastocyst are termed human embryonic stem cells (hESCs), and such cells were successfully derived and cultured for the first time in 1998 (Thomson et al., 1998). Subsequently, novel techniques developed by Yamanaka and colleagues in 2007 allowed for an alternative route to generate pluripotent stem cells, through reprogramming of somatic cells with a cocktail of four transcription factors (Takahashi et al., 2007; Takahashi & Yamanaka, 2006). This technology paved the way for generating human induced pluripotent stem cells (hiPSCs) from any adult individual with the prospect of using such cells for human disease modeling and autologous cell transplantation. While adult somatic stem cells have been applied routinely for clinical cell transplantation of hematopoietic cells since the late 1970s (Juric et al., 2016) and for skin cells since the 1980s (Chen, Przyborowski, & Berthiaume, 2009), the use of embryonic-stage stem cells, such as pluripotent stem cells, is a technology which is newer in development and which required several years of optimization and refinement of differentiation conditions before the technology would become ready for clinical use. Therefore, hPSC-based products are still only in early clinical phases, and none of those cell products have yet reached Phase III or market authorization (Christiansen & Kirkeby, 2024). Following several years of optimizing protocols for controlling the differentiation of hPSCs, there are today ongoing clinical trials for PD using both hESC- and hiPSC-derived products as well as also a product generated from human parthenogenetic pluripotent stem cells (hParPSCs).

4. Pluripotent stem cell products for PD

4.1 Protocols for differentiation of DA cells from hPSCs

Over the course of 10–15 years, protocols for derivation of midbrain DA neurons have gradually evolved through iterative protocol optimization. Initially, neuronal differentiation protocols involved neural induction into rosette-like structures on feeder cells, and this process could be enhanced by the addition of the neuralising factor Noggin (Elkabetz et al., 2008). Seminal work by the group of Lorenz Studer showed in 2010 that neuralization could be significantly enhanced in both speed and efficiency by the simultaneous blockage of SMAD pathways through a combination of a (TGF) Transforming growth factor)-beta inhibitor (often SB431542) and a BMP (Bone morphogenic protein) inhibitor (often Noggin, dorsomorphin or LDN193189), the so-called dual SMAD approach (Chambers et al., 2009). As the midbrain DA neurons are derived from the floor plate of the embryonic mesencephalon (Arenas, Denham, & Villaescusa, 2015; Arenas, Salto, & Villaescusa, 2015), further work was needed to optimize patterning of the progenitors into this specific domain. Studies from several labs showed that a delicate combination of a high-potency form of the ventralising morphogen SHH (sonic hedgehog) together with a tightly regulated dose of a GSK3 inhibitor (CHIR99021) to activate posteriorizing WNT signaling could efficiently generate high-purity cultures of ventral midbrain progenitor cells positive for FOXA2 (Forkhead box protein A2), LMX1A (LIM homeobox transcription factor 1 alpha) and OTX2 (Orthodenticle homeobox 2) (Kirkeby, Nelander, & Parmar, 2012; Kriks et al., 2011). Additional to this, some protocols apply local posteriorizing signals such as FGF8b (Fibroblast growth factor) or high-dose pulses of WNT to fine-tune patterning of the midbrain progenitors toward the DA-producing caudal midbrain domain expressing EN1 (Engrailed-1) (Doi et al., 2020; Kirkeby et al., 2017; Nolbrant, Heuer, Parmar, & Kirkeby, 2017). To push the progenitor cells out of cell cycle and toward neuronal maturation, most protocols apply neuronal maturation factors around day 10–20 of differentiation. These include Brain-derived neurotrophic factor (BDNF), GDNF, ascorbic acid, cyclic AMP and the notch inhibitor DAPT. When applied for transplantation, it is crucial that the cells are harvested at the right time to ensure proper patterning (i.e., if the cells are harvested too early, they may be insufficiently patterned and may generate off-target cells) as well as to ensure proper survival and

integration (i.e., if the cells are harvested too late, they may have poorer survival and integration capacity).

For the ongoing clinical trials, cell products are harvested for transplantation between day 16–30, and where some products are transplanted directly upon harvest (i.e., as fresh products), others are cryopreserved and stored before transplantation. While cryopreservation of the cell product may cause some loss in cell viability, the advantage of this approach is that the product can be manufactured in larger batches which can be quality controlled in vitro and in vivo prior to transplantation.

4.2 hESC-derived products for PD cell therapy

As of May 2024, three hESC-derived DA cell products are in clinical trials: (1) the Bemdaneprocel product by BlueRock Therapeutics, which has successfully completed its 12-month primary safety endpoint on 12 patients in the US and Canada; (2) the STEM-PD product by Lund University which entered into clinical trial for 8 patients in December 2022 (Sweden and UK), is still ongoing and has recently been approved for dose escalation and (3) the TED-A9 product by S. Biomedics, which has been dosed to 12 patients in a Phase I/IIa study in Korea (S Biomedics Co Ltd, 2024) (see Tables 1 and 2 and sections below). For all three products, the transplanted cells are cryopreserved progenitors which are not yet committed to the mature neuronal stage.

Table 1 Overview over the different cell products in clinical trials.

	STEM-PD	BlueRock Therapeutics	Kyoto Trial	MGH trial	S. Biomedics	Aspen Neuroscience
Cell source	ESCs	ESCs	iPSC (allo)	iPSC (auto)	ESCs	iPSC (auto)
Cryopreservation	YES	YES	NO	NO	at day 19	YES
Days of differentiation	16	16	30	28	25	18
Injected cell product	Single cells	Single cells	Cell aggregates	Single cells	Single cells	Single cells
Factors for neural induction	Noggin, SB	LDN, SB	LDN, A 83-01	LDN, SB	Dorsomorphin SB	LDN, SB
Factors for midbrain floor plate patterning	SHH, CHIR, FGF8b	SHH, CHIR (boost)	Purmorphamine, FGF8, CHIR	SHH, Purmorphamine, FGF8, CHIR	SAG, CHIR	SHH, purmorphamine, CHIR
Ref	(Kirkeby et al., 2023)	(Kim et al., 2021; Piao et al., 2021)	(Doi et al., 2020)	(Schweitzer et al., 2020)	(Park et al., 2024)	(Hills et al., 2023)

ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells; LDN, LDN193189; SB, SB431542; SHH, sonic hedgehog; FGF8, fibroblast growth factor 8; CHIR, CHIR-99021.

Table 2 Overview over clinical trials using DA cells from stem cells in PD.

	STEM-PD	BlueRock Therapeutics	Kyoto Trial	MGH	S.Biomedics	Aspen Neuroscience
Trial site	Lund (SE) Cambridge (UK)	New York (US), UC Irvine (US) Toronto (CA)	Kyoto (JP)	Boston (US)	Seoul, Korea	NY, CA, Arizona (US)
Clinical Trial ID	NCT05635409	NCT04802733	UMIN. 000033564	N/A	NCT05887466	NCT06344026
Nr of subjects	8	12	7	1	12	9
Disease duration	>10y	>3y - <20y	>5y	>10y	>5y	>4y
Dose: 10^6 cells per putamen (low/high dose)	3.5 / 7.1	0.9 / 2.7	2.4 / 4.8	4	1.58 / 3.15	no dose available
Delivery method	Stereotactic injection with Lexell frame. 5 tracts per putamen, 4-8 deposits per tract	MRI-guided Clearpoint system. 3 tracts per putamen, 3 deposits per tract	Stereotactic injection with Brainlab Elements and Lexell frame. 3 tracts per putamen, 4-8 deposits per tract	Stereotactic injection with Brainlab iPlan and Lexell frame. 3 tracts per putamen	3 tracts per putamen and 3 deposits/tract	Custom device, MRI guided injection
Immune suppression	Tacrolimus, Basiliximab, Azathioprine, Steroids	Tacrolimus, Basiliximab, Steroids	Tacrolimus	N/A	Yes (not described in detail)	N/A
PET imaging	F-DOPA, PE2i	F-DOPA	F-DOPA, GE180, FLT	F-DOPA	FDG; F-FP-CIT	F-DOPA
Primary endpoint	1 y	1 y	2 y	N/A	2 y	1 y
Observation period	3 y	2 y	2 y	2 y	5 y	5 (-15 y)
Expected time for primary endpoint	2025	2023	2023	Reported 2020	2026	2025
Reference	(Kirkeby et al., 2023)	(BlueRock_Therapeutics, 2024; Piao et al., 2021)	(CiRA, 2023; Takahashi, 2020)	(Schweitzer et al., 2020)	(Park et al., 2024; S Biomedics Co., 2024)	(Aspen_Neuroscience_Inc, 2023, 2024)

ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

The **Bemdaneprocel** product by BlueRock Therapeutics is a cryopreserved cell suspension of day 16 ventral midbrain DA progenitor cells produced from the H9 cell line from WiCell (hPSCReg WAe009-A). The differentiation protocol for the Bemdaneprocel product involves a "CHIR boost" step from day 7 to 10 to induce a peak of WNT pathway activation in the cells, for the purpose of inducing EN1 expression, and the cells are then matured for 6 days in maturation factors: BDNF, GDNF, cAMP and DAPT (Kim et al., 2021). This cell line has been tested preclinically and cell transplants survived and demonstrated amelioration of motor symptoms in multiple animal models of PD (Kriks et al., 2011). Moreover, optogenetic studies demonstrated that effects on motor symptoms were based upon DA release from the transplanted cells (Steinbeck et al., 2015). Extensive preclinical studies in rat and mouse models supported safety and proof-of-concept efficacy of the Bemdaneprocel product (Piao et al., 2021).

The **STEM-PD** product is produced from the RC17 hESC line from Roslin Cells in Edinburgh, UK (hPSCReg RCe021-A). As the BlueRock product, this cell product also consists of ventral midbrain DA progenitor cells cryopreserved on day 16 of differentiation (Kirkeby et al., 2023). The product is produced through an intitial combination of SHH and CHIR, followed by timed addition of FGF8b from day 9 to 16 to induce caudalization and EN1 expression in the progenitors for obtaining improved in vivo efficacy (Kirkeby et al., 2017; Nolbrant et al., 2017). Extensive 6–9 month preclinical studies of the STEM-PD product in nude rats demonstrated favorable safety and efficacy of the transplanted cells with minimal biodistribution outside of the transplanted site (Kirkeby et al., 2023).

The S. Biomedics product **TED-A9** is derived from the Korean GMP hESC line SNU-hES32 (Park et al., 2024). The differentiation protocol for TED-A9 involves the combination of dual SMAD inhibition together with CHIR and an SHH agonist to generate DA progenitor cells. This protocol involves an intermediate cryopreservation step at day 19, upon which the cells are quality controlled and thawed for terminal expansion into the cell product which is harvested for transplantation on day 25 (Park et al., 2024). Preclinical studies with the cell product showed good safety and efficacy in immunodeficient rats and included also PET imaging for F-DOPA (Park et al., 2024).

4.3 hiPSCs-derived products for PD cell therapy

As an alternative to blastocyst-derived hPSCs, the technology of iPSC was established by Yamanaka et al. in 2006 by introducing four reprogramming factors, Oct3/4, Nanog, KLF4, and c-Myc, to mouse fibroblasts (Takahashi & Yamanaka, 2006). In 2007, the technology was applied to human fibroblasts, and human iPSCs were established successfully (Takahashi et al., 2007). Since then, methods for establishing human iPSCs have been further improved. Initially, the original material of somatic cells was skin fibroblasts, but now peripheral blood cells are usually the preferred cell source. c-Myc, which was initially used as one of the reprogramming gene combinations, has subsequently been replaced by other genes to reduce the risk of tumorigenicity (Nakagawa et al., 2014) and the method for gene delivery has changed from the original retroviral vectors to mRNA (Mandal & Rossi, 2013), episomal vectors (Okita et al., 2011) or Sendai virus (Fusaki, Ban, Nishiyama, Saeki, & Hasegawa, 2009).

These methods avoid integration of the induced genes into the genome, which greatly improves safety for the clinical application. In addition, the primitive protocol needed co-culture of mouse stromal cells as feeders in the culture medium contained animal-derived components. Now a feeder-free technology (Nakagawa et al., 2014) has been established that allows culture from establishment to maintenance in xenofree culture media. As iPSCs are established from somatic cells, there are several advantages over ESCs. First, donor tissue such as blood or skin fibroblast is more easily accessible as there is no need to use IVF-derived blastocysts. Second, iPSCs enable autologous transplantation without the risk of rejection, if they are established from the patient's own somatic cells (Morizane et al., 2013; Schweitzer et al., 2020). Third, many cell lines can be easily established from pre-screened donors, making them suitable for cell banks. In Japan, a bank of human leukocyte antigen (HLA)-homozygous iPSCs has been established from HLA homo donors. To enable HLA-matched transplants for clinical use, HLA homo iPSCs are established from their somatic cells under conditions that meet GMP standards (Umekage, Sato, & Takasu, 2019). HLA is a protein expressed on the cell surface and plays a major role in immune rejection in organ transplantation. In bone marrow transplantation, it is known that matching HLA-A, -B and -DR haplotypes results in better outcomes. In Japan, an iPSC haplobank with three homologous HLA loci (HLA-A, -B and -DR) has been generated from seven donors and is estimated to be matched for 40% of the Japanese population (Yoshida et al., 2023). A study of iPSC-derived DA neural transplants into the brain of macaques reported a decrease of the immune response with matched transplants (Morizane et al., 2017). Recently, there are projects to create iPSC stocks by gene-editing HLA molecules and establishing hypoimmunogenic iPSCs or "universal cells." A study from Dr. Hotta's group estimated that more than 90% of the worldwide population would be covered if only 12 iPSC lines of hypoimmunogenic iPSCs were properly prepared (Xu et al., 2019). On the other hand, there are some disadvantages of iPSCs: (1) the risk of contamination of poor-grade stem cells by inappropriate reprogramming, (2) the risk of tumorigenesis in the case of any genome insertions of induced factors, and (3) disease susceptibility in the case of patient-derived autologous iPSCs. For example, the iPSCs originating from somatic cells with a genetic background of PD might have viability problems in the Parkinsonian brain environment after transplantation (Nguyen et al., 2011). In such cases, iPSCs derived from healthy volunteers should be used instead of an

autologous strategy. As well as ESCs, iPSCs are now being used clinically as a starting material for donor cell production in various clinical situations. As of 2023, there were 23 hiPSC-derived products in clinical trials worldwide, including for PD, age-related macular degeneration, retinitis pigmentosa, heart failure, spinal cord injury, osteoarthritis, thrombocytopenia and cancer (Kobold et al., 2023). As for PD, Kim et al. reported the first autologous transplantation case in the US with the result of graft survival and safety (Schweitzer et al., 2020). Aspen Neuroscience developed an autologous cell therapy product based on Sendai virus reprogramming into hiPSCs and differentiation using dual SMAD inhibition combined with CHIR, SHH and an SHH agonist (Hills et al., 2023). The company is now conducting the autologous cell therapy planned for eight PD patients in the United States, and dosing of the first patient took place in April 2024 (Aspen_Neuroscience_Inc, 2024). The FDA has granted Fast Track Designation for phase 1/2a trial for Aspen's cell therapy product, ANPD001, in the United States (Aspen_Neuroscience_Inc, 2023).

Using an allogenic iPSC approach, the Kyoto trial has been completed for seven patients. The cell product for the Kyoto trial is derived from an hiPSC stock established from a healthy homozygous donor carrying the highest frequency of Japanese HLA subtypes. In the donor cell production, target cells were differentiated toward floor plate fates with purified by cell sorting with an antibodiy against the floor plate marker CORIN at 12–13 days of differentiation, followed by sphere (cell aggregation) culture, and a total of 1-month-old spheres were used for transplantation. No cryopreservation steps were taken during the induction of donor cells from iPSCs. Sorting, no cryopreservation, and transplantation in the form of spheres are unique compared to the other two ESC trials for PD. Before the clinical trials, in vitro characterization of DA progenitors was carried out, confirming the absence of residual undifferentiated iPSCs, immature neural stem cells, and genetic mutations in cancer-related genes (Doi et al., 2020). For in vivo experiments, the safety of donor cells was confirmed in a tumor-forming assay in mice, and functional improvement was observed in PD model rats.

In the clinical study of the autologous transplant at Massachusetts General Hospital (MGH), the patient's own skin fibroblast-derived iPSCs were differentiated to DA progenitor cells. Similar to the other trials, dual SMAD approach with SB431542 and LDN193189 combined with midbrain floor plate patterning by CHIR, Shh, Purmorphamine and FGF8 were used. After treatment with quercetin, the final cell products at day 30 were transplanted.

4.4 hParPSC-derived products

In addition to the trials conducted with hESC and hiPSC products, an additional type of product, developed from human parthenogenetic cells (hParPSC) has also completed clinical trial. The hParPSCs are stem cells which have been generated through parthenogenesis of unfertilized oocyte by chromosomal duplication, This product (SC-HPNSC) is developed by the company International Stem Cell Corporation (ISCO), and consists of cortical-type PAX6-positive neural progenitor cells with a proposed trophic support effect (Garitaonandia et al., 2016; Gonzalez et al., 2016). The product has completed a dose-escalating Phase I clinical trial with 12 patients and the ISCO company has reported positive safety data from the first 6 patients in the low and medium dose cohorts (International Stem Cell Corporation, 2018), but not yet any data from the high dose cohort which was expected to be completed in 2020. It is important to note that the SC-HPNSC is not intended as a DA cell replacement product (i.e., it is not designed to generate mature DA neurons upon transplantation), but rather as a trophic support cell product which is hypothesized to inhibit cell death of the endogenous SN neurons. Therefore, this trial is not covered in the section below.

5. Overview over ongoing DA cell replacement clinical trials

5.1 ExPDite trial

The ExPDite clinical trial (Clinicaltrials.gov; NCT04802733) is an international phase I 24-month, open label, non-randomized, non-controlled study sponsored by BlueRock Therapeutics that completed enrollment in 2022. A total of 12 participants received 1 of 2 doses of bemdaneprocel delivered sterotactically to the bilateral post-commissural putamen and a 1-year immunosuppression regimen. The primary objective was to evaluate safety and tolerability at 1 year. Feasibility and exploratory clinical outcomes were also evaluated (Henchcliffe et al., 2023).

5.1.1 Cell product

Bemdaneprocel (cryopreserved allogeneic hESC-derived DA progenitors, day 16).

5.1.2 Recipients

Eligible individuals were aged ≥60 to ≤78 years in the United States and ≥50 to ≤78 years in Canada, with ≥3 to ≤20 years since PD diagnosis.

The minimum L-dopa response required for inclusion into the trial was at least 30% based upon MDS-UPDRS part III score, and participants met criteria of Hoehn & Yahr scale Stage 0–2 in the ON state and 3–4 in the OFF state in the United States, and 0–3 in ON state in Canada. For detailed eligibility criteria please see ExPDite_Trial (2022). Those enrolled had a median age of 67.0 (Q1, Q3: 64.5, 70.0, 5.4), and a mean duration of 9.1 (SD 3.2) years from time of PD diagnosis.

5.1.3 Transplantation

Donor cells were injected stereotactically to the recipients' bilateral putamens via three tracts per putamen with three deposits per tract. Two cohorts differed by cell dose delivered. The first 5 participants received a total of 0.9 million cells per putamen and the subsequent 7 participants enrolled received a dose of 2.7 million cells per putamen.

5.1.4 Immunosuppression

All recipients were immune suppressed with basilixumab intraoperatively and at day 4 postoperatively, IV prednisolone, then oral prednisone 5 mg daily and tacrolimus dosed to a plasma concentration of 4–7 ng/mL for 1 year after transplantation.

5.1.5 Assessments

The primary endpoint was the presence of adverse events (AEs) or serious adverse events (SAEs). The secondary endpoints included improvements in symptoms based upon UPDRS-III part 3 OFF, "on" and "off" time assessed by the Hauser Parkinson's Diary, and imaging biomarker outcomes (F-DOPA-PET changes from baseline up to 24 months). Multiple exploratory endpoints were included as part of this learning clinical trial, including ON and OFF time, dyskinesia rating scales, multiple non-motor outcomes and quality of life ratings.

5.1.6 Results

At 12 months post-transplantation, bemdaneprocel met pre-specified safety and tolerability criteria (Henchcliffe et al., 2023). Secondary and exploratory results supported the feasibility of stereotactic transplantation of bemdaneprocel, demonstrated increased 18F-DOPA uptake, and suggested stability or improvement in motor outcomes, more so in the higher dose cohort. Specifically, the high dose cohort showed a median improvement of 2.16 h in time spent in the "ON" state without troubling dyskinesia

compared with baseline after 1 year. Time spent in the "OFF" state showed a corresponding median decrease of 1.91 h after 1 year. Participants in the low dose cohort showed a median improvement of 0.72 h in the "ON" state without troubling dyskinesia time compared with baseline and a corresponding median decrease of 1.62 h in "OFF" state time. At 18 months post-transplant, 6 months after withdrawal of the immunosuppressive regimen, three SAEs had been recorded, only one of which was deemed related to surgery (seizure), and none were attributed to the cell product or immunosuppression. No graft-induced dyskinesia have been reported and dyskinesias did not increase. Improvement in MDS-UPDRS Part III and "OFF time" was maintained or increased in both cohorts. Importantly, 18F-DOPA-PET imaging demonstrated increased uptake in the bilateral putamen at 12 and 18 months (Henchcliffe et al., 2024; Sarva et al., 2024; Schmidt et al., 2024).

5.1.7 Next steps

Participants will enroll in an observational follow-up to 5 years, and a Phase II clinical trial is about to launch at the time of writing.

5.2 STEM-PD trial

STEM-PD (Clinicaltrials.gov; NCT05635409) is an academic international first in human, phase I/IIa, multicenter, single arm, dose escalation, advanced therapy medicinal product (ATMP) trial. The sponsor of the clinical trial is Region Skåne (Lund, Sweden) and patients are recruited at two clinical sites, Skånes University Hospital, Lund, Sweden, and at Cambridge University Hospital, UK.

All surgeries are performed at Skånes University Hospital, Lund, Sweden using the in house manufactured non-CE marked Rehncrona-Legradi device that has previously been used in the TransEuro trial in Sweden.

5.2.1 Cell product

STEM-PD (cryopreserved allogeneic hESC-derived DA progenitors, day 16).

5.2.2 Recipients

Patients with moderate PD and fluctuating disease but who have not yet reached the more severe advanced phase of the condition with uncontrollable motor fluctuations are recruited corresponding to Hoehn/Yahr stage 2–3 in OFF state. The choice of study population is motivated by the

investigators as a more advanced patient population is considered less likely to benefit from cell replacement treatment.

Eight patients aged 50–75 years and a disease duration >10 years are recruited from the previous TransEuroTrial observational cohort of patients with PD, who are well known to the investigators and have been clinically followed at the recruiting centers for >10 years. For detailed eligibility criteria please refer to (STEM-PD_Trial, 2024).

5.2.3 Transplantation

Participants undergo in an open label fashion transplantation of the STEM-PD cell product in a single dose/patient administered to the putamen by bilateral stereotaxic implantation.

The cell product clinical batch has been produced at the Centre for Cell, Gene & Tissue Therapeutics (CCGTT), Royal Free Hospital in London under reguations for good manufacturing practice (GMP). STEM-PD has been quality controlled, released, imported and shipped to Lund (Kirkeby et al., 2023) and prepared by a trained cell biologist at the clinical site immediately prior to transplantation.

Dose extrapolations are calculated based on potency studies in animal models and the expected number of surviving DA neurons/putamen. Participants receive one of two doses:

- Dose 1: 3.54×10^6 STEM-PD cells grafted per putamen (aiming at 100,000 surviving DA cells/putamen)
- Dose 2: 7.08×10^6 STEM-PD cells grafted per putamen (aiming at 100,000 surviving DA cells/putamen)

Dosing is performed in a staggered fashion. Six months after dose 1, safety and imaging data were reviewed by the independent data safety and monitoring board (DSMB) and the dose escalation for the next four participants was recently approved.

5.2.4 Immunosuppression

The triple immunosuppressant regime used in the STEM-PD trial matches the regime that is used as standard in organ transplant practice, but the post-transplant period of immunosuppression is limited to 1 year. The duration of immunosuppression is motivated by previous clinical trials with fetal DA cells in PD that have shown that after this point grafts appear to survive indefinitely without any further immunosuppression (Li et al., 2016).

Immunosuppression is started the day before surgery, continued for 12 months post-transplant and then tapered off over 3 months. Patients receive Tacrolimus adjusted to blood levels, Azathioprine, and Prednisolone and in addition 1 g IV methyl prednisolone sodium succinate as a one-off dose at the time of surgery. Basiliximab is given at a dose of 20 mg IV at the day of surgery and day 4 post-transplant.

5.2.5 Assessments

The primary objective of this trial is to assess the safety, tolerability and feasibility of bilateral intraputamenal transplantation of the STEM-PD product in patients with moderate PD. This is assessed by the number and nature of AEs and SAEs in the first 12 months following transplantation and the absence of space occupying masses on cranial MRI in the first 12 months following transplantation.

Secondary objectives include to evaluate the course and efficacy on the clinical features post-transplantation; to assess the survival and maturation of dopamine cells following transplantation using PET imaging and to determine the safety and clinical efficacy between doses of the STEM-PD product including assessment of whether there is a dose response effect.

Changes in clinical effects at 36 months following transplantation will be compared to baseline using a range of standardized motor tasks, and cognitive and neuropsychiatric tests and include any emergence of new neurological features such as GID's, global cognitive changes and changes in non-motor/Quality of Life (QOL) assessments. In addition, changes in motor features in the OFF state, changes in anti-Parkinson medication measured by L-Dopa equivalent dose (LED) and any changes in F-DOPA uptake and DA transporter (DAT) binding at 36 months on PET imaging using the ligands ^{18}F-DOPA and ^{18}F-PE2I compared to baseline are measured.

Also, the number and nature of SAEs and AEs in the 12–36 months period following transplantation is recorded.

5.2.6 Results

The study is ongoing and results are expected to be reported in 2028.

5.3 TED-A9 study

This ongoing clinical trial sponsored by S. Biomedics Co., Ltd. is a single center trial performed at Yonsei University Health System, Severance Hospital, Seoul, Republic of Korea. This is an open label, dose-escalation,

phase I/IIa study to evaluate the safety and exploratory efficacy of the hESC-derived A9 Dopamine progenitor cell (A9-DPC) therapy in patients with PD (Clinicaltrials.gov; NCT05887466). The study started in May 2023 and is expected to be completed in 2026.

5.3.1 Cell product

TED-A9 (allogeneic hESC-derived DA progenitors, day 25).

5.3.2 Recipients

Twelve patients with fluctuating idiopathic PD with a disease duration of >5 years exhibiting motor complications such as drug wearing-off, freezing of gait or dyskinesia and aged between 50 and 75 years were included in the study.

For detailed eligibility criteria please refer to TED-A9_Trial (2024).

5.3.3 Transplantation

TED-A9 were administered to 6 participants in the low-dose group (3.15 million cells) and to another 6 participants in the high-dose group (6.30 million cells) or 1.58 million cells/3.15 million cells per putamen, respectively. The procedure was performed in a single session using 3 tracts/putamen and distributing the cells in 3 deposits per tract.

Dosage:

- 1st Stage Dosage: 3.15×10^6 cells/body (6 tracks in total, 52.5×10 ^4 cells per track)
- 2nd Stage Dosage: 6.30×10^6 cells/body (6 tracks in total, 105×10 ^4 cells per track

5.3.4 Immunosuppression

No information on immunosuppression has been published.

5.3.5 Assessements

The primary endpoint of the trial is the occurrence of treatment-emergent AEs, transplant failure/rejection, bleeding and infection as well as AESI's such as (a) death, (b) generation of a neoplasm or malignant tumor in tissues or organs, (c) onset of an immune reaction including worsening of a previous autoimmune disease or new occurrence, and (d) other delayed AEs related to this embryonic stem cell treatment at 2 years after transplantation.

Secondary exploratory outcome measures include changes in motor scores, cognition, neuropsychological measures, quality of life and non-motor

symptoms at 2 years after grafting. Patients are frequently examined using MRI, Fluorodeoxygkucose (FDG)-PET and FP-CIT PET.

5.3.6 Results

Biomedics recently announced that all 12 participants have received a transplant. No safety or efficacy data are available yet. The study is expected to deliver the primary endpoint results in 2026 and the study is completed in 2029.

5.3.7 Next steps

The study will continue to follow patients for 2 years after grafting with an additional 3 years observation.

5.4 Kyoto trial

A clinical trial of human iPSC-derived DA neural progenitor cell transplantation has been conducted in Japan since 2018 (UMIN. 000033564). The aim of the trial was the evaluation of safety and efficacy of the transplantation of allogenic human iPSC-derived DA neural progenitor cells in PD patients. This trial was a single-arm, non-randomized and open phase I/II study. The target sample size was seven cases (Barker, Parmar, Studer, & Takahashi, 2017; Takahashi, 2020).

5.4.1 Cell product

hiPSC-derived CORIN-sorted DA spheroids, day 30.

5.4.2 Recipients

The recipient criteria were similar to those in the other two trials: namely, subjects who were uncontrollable by medical treatment alone, aged 50–69 years, had a diagnosis of PD of at least 5 years, met Hoehn & Yahr scale Stage III-V (OFF), I-III (ON) and were responsive to L-dopa (>30%) (for detailed eligibility criteria see Kyoto-Trial (2024)).

5.4.3 Transplantation

Under general anesthesia, approximately 2.4 or 4.8 million donor cells per putamen were injected stereotaxically. The cells were injected as spheres with a diameter of about 400 mm. Before the procedure, surplus spheres were enzymatically dissociated and counted to approximate the number of cells per sphere. The spheres were injected through three tracts per side. A newly developed needle suitable for a stereotaxic device was used for the injection.

5.4.4 Immunosuppression

The iPSC line for this trial was estimated to match 17% of the Japanese population, but no intentional HLA matching was performed in the candidate selection. Instead, all recipients were immune suppressed with tacrolimus for approximately 1 year after transplantation. Tacrolimus blood levels were monitored, and GE180-PET scan was performed periodically to detect any potential immune rejection.

5.4.5 Assessment

The primary endpoint was the presence of AEs or SAEs. The secondary endpoint was improvements in symptoms as assessed by UPDRS-III, length of daily off period, PDQ39, cognition as measured by MMSE (Mini Mental State Examination). Functional brain imaging, PET scans (F-dopa, FLT (fluorothymidine), GE180 (Flutriciclamide), were performed regularly.

5.4.6 Results

The study was finished in 2023 and the results are expected to be reported in 2024.

5.4.7 Next steps

An application will be submitted for approval of conditional and time-limited marketing authorization in Japan.

An investigator initiated-clinical study with the same cell product (CT1-DAP001, Phase1/2) will be started at UC San Diego supported by Kyoto University and Sumitomo Pharma Co., Ltd. (CiRA, 2023).

5.5 ASPIRO trial

The ASPIRO trial is a phase I/II a open label clinical trial to assess safety and tolerability of ANPD001, an autologous, DA neuron cell replacement using the patients own skin-derived fibroblasts as starting cell. The trial is sponsored by Aspen Neuroscience, a private biotechnology company in the United States.

5.5.1 Cell product

Autologous hiPSC-derived DA progenitors, day 18 (ANPD001).

5.5.2 Recipients

The study population comprises 9 subjects with moderate to severe PD, aged 50–70 years. For detailed inclusion/exclusion criteria of the ASPIRO trial please see: ASPRIRO_Trial (2024).

5.5.3 Transplantation

Transplanation of the cell product in a single cell suspension is performed by MRI-guided stereotaxic injection using a custom device to facilitate slow injection of small volumes of investigational drugs. No information on dosing schedules was available.

5.5.4 Immunosuppression

Not applicable.

5.5.5 Assessments

The primary study endpoint of this phase I/IIa trial is safety and tolerability of two sequentially escalating doses of the cell product measured by the incidence and severity of treatment emergent adverse events (TEAE) and SAEs at 1 year post transplantation.

Secondary endpoints include motor assessments and quality of life rating scales assessed at 5 years. Patients are further followed via telephone interviews for an additional 10 years to capture late-emerging effects or side effects of the intervention.

5.5.6 Results

Aspen announced in April 2024 the transplantation of the first patient at Banner-University Medical Centre in Tucson, University of Arizona College of Medicine, the lead dosing site for the ASPIRO study (Aspen_Neuroscience_Inc, 2024).

5.5.7 Future outlook

Primary endpoint results are estimated in 2025 and study completion in 2030.

6. Outlook and opinion leader conclusion

Cell therapy for PD is now one of the most exciting and promising future therapeutic options that has entered clinical trials and is moving toward market authorization. While all trials are still in phase I/IIa, thus far the preliminary safety assessments and early efficacy indicators look very promising.

No matter what the final outcome, important lessons will be learned from these early trials and will provide key knowledge for the improvement of trial design and optimization of the cell products.

One of the remaining hurdles to be overcome in the future is the need for immunosuppression of patients receiving allografts. The personalized approach using autologous iPSC is attractive from an immunological perspective, however, potential drawbacks connected to disease susceptibility of the cells, high costs and logistic challenges remain to be fully understood. In order to further develop autologous cell lines for clinical use at a large scale, efforts are currently being made to develop hypoimmune universal cell lines by genetic engineering that would be able to escape the recognition of the immune system. These cells need to be tested clinically. Also, efforts to achieve better graft survival, and even more efficient DA differentiation with robust and reproducible protocols are still ongoing.

For cell therapy to become a globally available treatment, cell products need to be scalable. This includes storage of large cell numbers and cryopreservation, both of which need further investigation.

It is critical in this phase of rapid technological advances that communication and transparency is maintained to benefit the field as a whole. With multiple research teams now translating their findings into first in human clinical trials, there is a need for some guiding principles. A global effort to harmonize work between the different consortia working on the development of stem cells for clinical trials in PD was the foundation of G-Force (http://www.gforce-pd.com). GFORCE is a platform allowing key leaders in the field to work more closely together, exchange experience and discuss critical issues while maintaining their own individual identities and working according to their national regulatory needs. This may serve as a model for moving ahead, balancing the needs of individual research teams and development programs, with an overarching goal of bringing superior therapeutics in the future to those with PD.

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Cover image: Kateryna Kon (Shutterstock)

ISBN 978-0-443-31468-1

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