Combined cell-based therapy strategies for the treatment of Parkinson’s disease: focus on mesenchymal stromal cells

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Abstract

Parkinson’s disease is a neurodegenerative condition characterized by motor impairments caused by the selective loss of dopaminergic neurons in the substantia nigra. Levodopa is an effective and well-tolerated dopamine replacement agent. However, levodopa provides only symptomatic improvements, without affecting the underlying pathology, and is associated with side effects after long-term use. Cell-based replacement is a promising strategy that offers the possibility to replace lost neurons in Parkinson’s disease treatment. Clinical studies of transplantation of human fetal ventral mesencephalic tissue have provided evidence that the grafted dopaminergic neurons can reinervate the striatum, release dopamine, integrate into the host neural circuits, and improve motor functions. One of the limiting factors for cell therapy in Parkinson’s disease is the low survival rate of grafted dopaminergic neurons. Different factors could cause cell death of dopaminergic neurons after grafting, such as mechanical trauma, growth factor deprivation, hypoxia, and neuroinflammation. Neurotrophic factors play an essential role in the survival of grafted cells. However, direct, timely, and controllable delivery of neurotrophic factors into the brain faces important limitations. Different types of cells secrete neurotrophic factors constitutively and co-transplantation of these cells with dopaminergic neurons represents a feasible strategy to increase neuronal survival. In this review, we provide a general overview of the pioneering studies on cell transplantation developed in patients and animal models of Parkinson’s disease, with a focus on neurotrophic factor-secreting cells, with a particular interest in mesenchymal stromal cells; that co-implanted with dopaminergic neurons would serve as a strategy to increase cell survival and improve graft outcomes.

Key Words: brain repair; cell replacement; co-grafts; dopaminergic neurons; fetal ventral mesencephalic tissue; mesenchymal stem cells; neural grafting; neural transplantation; neuroblasts; neurotrophic factors

Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the presence of motor manifestations such as tremor, rigidity, bradykinesia, and postural instability and a variety of non-motor symptoms that include sensory abnormalities, autonomic dysfunction, sleep disturbances, fatigue, apathy, and psychiatric disorders (Armstrong and Okun, 2020). PD pathology mainly lies in the degeneration of dopaminergic neurons in the substantia nigra (Poewe et al., 2017). Although there is a wide range of pharmacological treatments for PD, all treatments currently available provide only symptomatic relief. Levodopa is the most potent and effective treatment and remains as the gold standard. However, the beneficial effect of levodopa gets progressively shorter throughout the disease, and prolonged treatment is associated with drug-induced dyskinesia and other disabling side effects that limit its use (Armstrong and Okun, 2020; Lopez-Lopez et al., 2021). With a relatively localized neural degeneration, PD is considered a good target for cell therapy (Fan et al., 2020). Over nearly four decades, different restorative surgical therapies have emerged to replace lost dopaminergic neurons. First clinical trials based on intrastriatal transplantation of human fetal ventral mesencephalic (FVM) tissue showed that grafted cells survive and induce significant, long-lasting improvements in motor symptoms (Lindvall et al., 1990), although possible effects on non-motor symptoms were not explored. However, the low availability of human mesencephalic tissue limited its use. Currently, stem cells represent a promising alternative source for the generation of dopaminergic neurons (Jang et al., 2020; Rahimpour et al., 2022). In addition to important issues such as defining an optimal cell source, better criteria for PD patient selection, improved and standardized protocols, avoiding rejection, and promoting functional integration (Rahimpour et al., 2022), other factors that compromise the survival of grafted dopaminergic neurons, such as mechanical trauma, growth factor deprivation, hypoxia, oxidative stress, and neuroinflammation need to be addressed (Brundin et al., 2000; Moriarty et al., 2017). Low dopaminergic survival can be partially counteracted by neurotrophic factor addition. Although different strategies have been studied, direct, timely, and controllable delivery of neurotrophic factors into the brain faces important challenges (Gantner et al., 2020; Studer and Tabar, 2020). Different types of cells secrete neurotrophic factors constitutively and co-transplantation of these cells with dopaminergic neurons represents a feasible strategy to increase neuronal survival. In this review, we focus on the co-grafting of dopaminergic neurons and neurotrophic factor-secreting cells, with a particular interest in mesenchymal stromal cells (MSCs), as a possible strategy to reduce cell death after grafting, which represents one of the drawbacks faced by cell therapy to make the definitive leap to the clinic (Figure 1).

Search Strategy and Selection Criteria

The search strategy and selection criteria were limited to articles published in peer-reviewed journals. A literature review of articles published in English from inception up to April 2022 was conducted by searching in the National Library of Medicine (PubMed) database (https://pubmed.ncbi.nlm.nih.gov/) using the following keywords: fetal ventral mesencephalic tissue, graft, Parkinson’s disease, co-grafts, mesenchymal stromal/stem cells, transplantation, neuroblasts, survival, embryonic stem cells, pluripotent induced stem cells and combination of the above terms. We also revised references of eligible articles.

Historical Overview

In 1975, Seiger and Olson grafted fetal brain tissue into the anterior eye chamber, laying the groundwork for future transplants in the nervous system. Cells derived from FVM tissue, enriched in dopaminergic cells, were the first type of cells transplanted in an animal model of PD. These initial preclinical
studies confirmed that dopaminergic grafts were able to survive, extend projections into the host striatum and ameliorate behavioral deficits in dopamine-depleted animals (Bjorklund et al., 1980). Such was the impact of these results that in the early 1980s, the first PD patients in the world received intracerebral grafts. However, these patients were grafted with autologous chromaffin cells obtained from the adrenal medulla, which had also been used in animal models of PD, to avoid the practical and ethical issues associated with human fetal tissue (Freed et al., 1981). Although it was initially assumed that adrenal medulla and FVM cells had similar mechanisms of action based on dopamine production, further studies showed that adrenal medulla graft benefits were due to neurotrophic actions that promote the sprouting of striatal dopaminergic fibers and not to dopamine production (Freed et al., 1990). However, the transient and highly variable improvements observed both in animal models and in PD patients, the frequent surgical complications, and the low cell survival observed in post-mortem studies led to the abandonment of the use of adrenal medullary tissue for transplantation (Date et al., 1990). A breakthrough in the field was the use of dissociated cell suspensions derived from FVM tissue, which permitted the targeting of deep structures as well as multiple graft placements (Bjorklund et al., 1983). A crucial step forward in clinical translation was the demonstration that dopaminergic neurons isolated from human embryonic/fetal tissue survive, provide extensive graft-derived striatal innervation, and ameliorate motor deficits after transplantation in preclinical models of PD (BRUNDIN et al., 1986). Based on almost 10 years of transplantation studies in animal models, the first patients receiving grafts of human FVM tissue were implanted in 1987 (Lindvall et al., 1990). This pioneering study demonstrated for the first time that FVM-based grafts can survive in a human brain affected by neurodegenerative disease and could restore dopamine levels, monitored in the striatum using [123I]-raclopride positron emission tomography, for as long as 10 years after surgery (Piccini et al., 1999). Interestingly, post-mortem studies carried out 24 years after grafting showed dense graft-derived innervation in the putamen (Hallett et al., 2014). The outcomes of a series of open-label trials showed promising results and generated high expectations in the field, leading the way to two National Institutes of Health-funded, double-blind, randomized, placebo-controlled trials. However, the results were disappointing, with some grafted patients showing normalized dopamine signaling while other participants showed modestly or no recovery compared to patients subjected to sham surgery (Freed et al., 2001). Nevertheless, even more discouraging was the fact that a subset of grafted patients developed graft-induced dyskinesias years later (Hagell et al., 2002), possibly due to the composition of the transplanted cell suspension. Experimental studies using different proportions of dopaminergic and serotonergic neurons in the cell suspension showed that higher proportions of serotonergic neurons, which are usually present in the graft, led to the dyskinesia, since serotonergic terminals could release dopamine as a false transmitter in an unregulated fashion (POLITIS et al., 2010). Additional evidence suggests that endogenous serotonergic neurons and serotonergic and dopaminergic interactions would contribute to the development of graft-induced dyskinesias (Muñoz et al., 2020). With the knowledge acquired in subsequent research, it is now considered that these studies were carried out prematurely and some of the side effects could have been avoided through careful selection of patients, improving the method of implantation and the composition of the grafted cell suspension, and optimizing the post-transplant immunosuppressive regimes (Bjorklund and Lindvall, 2017). The cumulative reanalysis of previous trials led a European research consortium called TRANSEURO to design a step-by-step optimized open-label trial, which is currently ongoing, with the main objective of developing an efficacious and safe methodology for FVM cell-based therapy for PD (ClinicalTrials.gov identifier NCT01898390) (Barker and TRANSEURO consortium, 2019).

Due to the abovementioned shortage of human FVM tissue for cell-based therapy and advances in stem cell knowledge, many efforts have focused on generating dopaminergic neurons for transplantation from stem cells, which potentially offer an unlimited number of cells. Different stem cell types have been considered as a possible source of neurons for the treatment of PD. However, the best positioned sectors to be employed remain those comprising induced pluripotent stem cells (iPSCs) (Jang et al., 2020). Notable advances in differentiation protocols have led to the achievement of highly pure dopaminergic neurons suitable for clinical trials that showed satisfactory therapeutic effectiveness of the grafted cells in PD and did not cause severe side effects in these animals (Xiong et al., 2021). The first transplantsations using clinically graded hiPSC-derived neurons have already been carried out (Schweitzer et al., 2020). Piao et al. (2021) have recently reported the generation of the first ESC-derived dopaminergic neurons for the treatment of PD, which was approved for a clinical trial in the United States (Takahashi, 2021; Figure 2). There is no doubt that stem cell technologies have the potential to be at the forefront of such PD treatments (Farivar et al., 2020). However, it should be noted that, beyond the motor symptoms, the disease exhibits non-motor symptoms that can be disabling for the patient, which currently are not targeted by cell therapy and should also be considered in future therapies (Pantcheva et al., 2015).

Despite the encouraging results obtained, cell-based therapies face important limitations and challenges. In addition to issues concerning safety and reproducibility, a critical aspect is the survival rate of the grafted dopaminergic neurons. Different evidence suggests that only 3–20% of grafted dopaminergic cells survive after the procedure (Brundin et al., 2000; Kim et al., 2020; Li and Li, 2021; HILLER et al., 2022). Triggers that may initiate dopaminergic cell loss in grafts include mechanical trauma, neuroinflammation, poor vascularization, and growth factor deprivation in the host brain (Barker et al., 1996; Brundin et al., 2000; Moriarty et al., 2017). The critical interval during which most dopaminergic cells die is the first few days after transplantation (SORTWELL et al., 2000). The idea of utilizing cells with neurotrophic properties to modify the pathologic brain environment or promote neuroprotective effects has been appearing on the horizon for central nervous system disorders. In the following section, we will review the most relevant studies in which combinations of dopaminergic grafts with other cells with supportive properties have been used as a strategy to overcome the poor survival of transplanted neurons (Figure 3).

Co-Grafting Strategies: A Review

Co-grafting strategies based on the combination of FVM tissue with cells with neurotrophic properties that could promote the survival of transplanted dopaminergic cells represent a therapeutic option to overcome the typical loss of 80–95% of the grafted dopaminergic neurons following transplantation. In the 1980s, the first studies exploring the benefits of peripheral nerve transplantation on the survival of dopaminergic grafts were carried out. Schwann cells, the principal glial cell type in the peripheral nervous system, are involved in neuronal survival and nerve regeneration (MA et al., 2021). Aghayev et al. (1984) demonstrated that transplanted FVM neurons in 6-hydroxydopamine (6-OHDA)-lesioned rats survived, and the combination of axonal guidance cues, neurotrophic factors, and growth factors provided additional support. Furthermore, it has been shown that co-grafts of FVM tissue with peripheral nerves or Schwann cells induced behavioral improvements and promoted axonal growth to the striatum compared to FVM grafts in rat models of PD (van Horne et al., 1991; TIMMERMANS et al., 2004). However, studies did not observe neuroprotective effects after co-transplantation of FVM tissue and saphenous nerve in lesioned monkeys (Collier et al., 1994). Offactory ensheathing cells (OECs) are another type of peripheral glial cells specialized in supporting continuous offactory nerve fiber growth throughout life. Co-culture of OECs with dopaminergic cells promoted dopaminergic neurite outgrowth (DENIS-DONINI and ESTENZO, 1988). Implantation of cultured OECs in dopamine-depleted rats after 6-OHDA
lesioning was not sufficient to promote tissue repair or functional recovery (Dewar et al., 2007). However, the combination of FVM with OECs enhanced the effects of grafted neurons in different rat models of PD (Agrawal et al., 2004; Johansson et al., 2005; Weng et al., 2017). Similar results were obtained when dopaminergic neurons isolated from porcine FVM cells or dopaminergic neurons derived from human stem cells were co-implanted with OECs (Shukla et al., 2009; Weng et al., 2020).

It is well-established that striatal cells exert both trophic and trophic effects that contribute to providing a target for mesencephalic dopaminergic neurons during the development of the nigrostriatal pathway (Barker et al., 2020). To extend these properties to cell transplantation, several works focused on studying the effects of co-grafting striatal cell suspensions with FVM tissue. In a ground-breaking study carried out by Brundin and collaborators, rat FVM cells were grafted alone or in combination with striatal (i.e., a major dopamine target area) or spinal cord (i.e., a non-target area) cells. The results showed that mixed mesencephalic and striatal suspensions gave rise to a greater area of dense dopaminergic innervation into the host striatum than grafts of FVM alone or FVM combined with spinal cord cells (Brundin et al., 1986). Similar results were obtained in subsequent studies, showing increased dopaminergic survival and maturation in recipients treated with differentiated rodents and monkeys after nigral-striatal co-grafts (Yurek et al., 1990; Costantini et al., 1994; Emgard-Matsson et al., 1997; Sortwell et al., 1998; Sluss et al., 2008). The effects of FVM and striatal grafting in a PD patient were also explored and the results showed improved motor function and a significant increase in the uptake of fluoro-L-DOPA detected by positron emission tomography in the co-grafted putamen (i.e., grafts of FVM and lateral ganglionic eminence tissue) compared to the non-co-grafted side (i.e., a graft of FVM tissue alone) (Lee et al., 2003). The discovery of glial cell line-derived neurotrophic factor (GDNF), which is expressed in the rodent striatum, as the most potent neurotrophin that promotes dopaminergic survival quickly, sparked interest in this factor in neuroprotective and cell therapies for PD. Previous studies showed that GDNF rescues dopaminergic neurons in animal models of PD (Winkler et al., 1996). Different approaches to delivering GDNF have been proposed to achieve a sustained release of minimum effective levels or to enhance the survival and fiber outgrowth from embryonic nigral cells grafted in 6-OHDA-lesioned rats (Wibb.ny, 1999). Carotid body glomus cells are highly dopaminergic and produce GDNF, and their neuroprotective and neuroreparative effects have been demonstrated in rodent PD models (Villagedio et al., 2005) and trialed in PD patients (Arjona et al., 2003). Our group in collaboration with Toledo-Aral’s team observed that the survival of dopaminergic neurons, the graft-derived dopaminergic innervation, and the performance of the cylinder test were improved in dopamine-depleted rats that received co-grafts of FVM and cell aggregates obtained from the carotid body compared to control groups that received FVM tissue alone (Rodriguez-Pallares et al., 2012). Other studies obtained similar results when different GDNF-producing cells such as fibroblasts, modified neural stem cells or myoblasts were co-grafted with dopaminergic neurons (Ostenfeld et al., 2002; Jinghong et al., 2005; Deng et al., 2013; Perez-Bouza et al., 2017). Transplantation of expanded neural precursor cells derived from the developing human brain was also explored in animal models of PD (Kim et al., 2003; Rodriguez-Pallares et al., 2005). Co-grafting VM-derived precursors with cultured astrocytes resulted in almost complete behavioral recovery and a higher number of tyrosine hydroxylase (TH)-positive cells within the graft, with longer fiber length compared to VM grafts alone. Indeed, grafted astrocytes exhibited region-specific heterogeneity in their secretory profiles, and the beneficial effects on graft survival and function were more evident when VM-derived precursors were co-implanted in the same suspension with VM-derived astrocytes. Other works proposed the use of 3D scaffolds/grafts (such as alginate, collagen, or hydrogels) to enhance the survival, maturation, and functional recovery of transplanted dopaminergic neurons. The beneficial effects derived from long-term delivery. Co-transplantation strategies have been proposed to achieve a sustained release of minimum effective levels or to enhance the survival and fiber outgrowth from embryonic nigral cells grafted in 6-OHDA-lesioned rats (Wibb.ny, 1999). Carotid body glomus cells are highly dopaminergic and produce GDNF, and their neuroprotective and neuroreparative effects have been demonstrated in rodent PD models (Villagedio et al., 2005) and trialed in PD patients (Arjona et al., 2003). 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IL-1β, and IL-6 and increased the levels of anti-inflammatory cytokines IL-4 and IL-10. Overall, MSCs have unique and valuable characteristics for the repair of the nervous system in various diseases including PD (d’Angelo et al., 2020).

Mesenchymal Stromal Cell-Based Therapies for Parkinson’s Disease

Different studies suggest that MSCs can differentiate into neural progenitors from which cells resembling dopamine neurons (i.e., that express the dopamine-specific marker H) can be obtained (Thompson et al., 2019). Neuronal-primed MSCs or dopaminergic cells derived from MSCs have been transplanted in animal models of PD (Delcroix et al., 2011; Park et al., 2012a; Shah et al., 2012; Greco et al., 2013). However, other studies have shown that MSCs can integrate into the host nervous system, and thus these cells can be used as a source of transplantable cells. Therefore, most studies have focused on their ability to produce a wide range of factors. Transplantation of murine BM-MSCs into the substantia nigra of intracerebral injected fVM cells was shown to improve the motor function of PD mice (Shetty et al., 2013; Wang et al., 2013). However, it is essential to control tightly the density of the transplanted cells or concentration of MSC-derived factors, since uncontrolled systemic delivery of MSCs is associated with a decrease in the therapeutic effects of MSCs. Not only are uncontrolled systemic effects of MSCs not only based on direct cell-to-cell interactions but that paracrine signaling seems to be a primary mechanism (Mendes-Pinheiro et al., 2019; Fricova et al., 2020).

As previously indicated, several mechanisms could be responsible for these effects. Our group observed that classical pathways involved in trophic factor-mediated signaling, such as MAPK/ERK and PI3K/Akt, were active in dopaminergic cultures (Parga et al., 2018). Other studies have shown that MSCs are a potential source of trophic factors acting at a systemic level, including the secretion of cytokines, growth factors, and other bioactive molecules (Thompson et al., 2019). The use of MSCs as a source of trophic factors acting at a systemic level could be a potential strategy for the treatment of PD.

Based on these promising results, several groups have conducted clinical trials using autologous or allogeneic MSCs isolated from various sources for PD (Fricova et al., 2020). In a pilot study, allogeneic BM-MSCs were transplanted unilaterally into the substantia nigra in seven PD patients (Park et al., 2010). Two years later, the same research group conducted another open-label study using autologous BM-MSCs implanted bilaterally in the substantia nigra (Park et al., 2012a). Although there were promising results, these studies lacked the power to draw definitive conclusions. In addition, these studies were conducted in an open-label setting, which may have confounded the interpretation of the results. Further research is necessary to understand the mechanisms underlying the therapeutic effects of MSCs and standardize experimental designs and protocols to achieve reliable and effective cell-based treatments for PD.

Conclusions and Future Perspectives

Over the decades, cell-based therapies have shown their potential in the treatment of PD. Although prematurely conducted trials in the past have cast doubt on the efficacy of these emerging approaches, human FVM tissue continues to be the gold standard and has undoubtedly paved the way for considering the clinical translation of transplantation of dopaminergic neurons obtained from different sources. The number of healthy dopaminergic neurons needed for functional improvements in PD patients is around 40,000–80,000 neurons. Several studies have shown that MSCs can survive and the cAMP-PKA pathway, used by many prostaglandins to mediate signaling, such as MAPK/ERK and PI3K/Akt pathways, were active in dopaminergic cultures (Parga et al., 2018).

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### Additional Table 1: Co-grafting-based strategies in Parkinson’s disease

| Reference             | Co-grafted cells                                                                 | Animal model                  | Outcomes                                                                 |
|-----------------------|----------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------|
| Aguayo et al., 1984   | Rat fVM tissue + rat sciatic nerve                                                | 6-OHDA Rat (female)           | ▪ Monoaminergic neurons within the graft extended axons along the nerve bridges |
| van Horne et al., 1991| Rat fVM tissue + rat sciatic nerve                                                | 6-OHDA Rat (male)             | ▪ Improvement in rotational behavior after co-grafting                    |
| Timmer et al., 2004   | Rat fVM cells (2-2.5 \(\times\) 10^5) + rat SC (2-2.5 \(\times\) 10^5) 8 wk post-lesion | 6-OHDA (MFB) Rat (female)    | ▪ Increased survival of DA cells in co-grafts                             |
| Collier et al., 1994  | Monkey fVM cells + monkey saphenous nerve 1 post-lesion                          | MPTP Monkey (male)            | ▪ No neuroprotective effects                                             |
| Agrawal et al., 2004  | Rat fVM cells (2.5 \(\times\) 10^5) + rat OECs (2.5 \(\times\) 10^5) Intrastratal | 6-OHDA Rat                   | ▪ Improvement in rotational behavior after co-grafting                    |
| Johansson et al., 2005| Rat fVM cells (1 \(\times\) 10^5) + rat OECs (2 \(\times\) 10^5) or rat astrocytes (2 \(\times\) 10^5) 4 wk post-lesion | 6-OHDA (MFB) Rat (female)    | ▪ Co-grafts with OECs enhanced DA survival and neurite elongation         |
| Weng et al., 2017     | Rat fVM cells (2 \(\times\) 10^5) + rat OECs (2 \(\times\) 10^5) Intrastratal 3 wk post-lesion | 6-OHDA (MFB) Rat (male)      | ▪ Co-grafted rats exhibited better motor recovery (rotometer) and enhanced survival of grafted DA cells |
| Shukla et al., 2009   | Rat fVM-derived NSCs (2.5 \(\times\) 10^5) + rat OECs (2.5 \(\times\) 10^5) 4 wk post-lesion | 6-OHDA (MFB) Rat (female)    | ▪ Restitution of motor function and increased survival and reinnervation of grafted NSCs |
| Weng et al., 2020     | Porcine fVM cells (2.5 \(\times\) 10^5) + rat OECs (2.5 \(\times\) 10^5) Intrastratal 2 wk post-lesion | 6-OHDA (MFB) Rat (male)      | ▪ Better improvement in apomorphine-induced rotational behavior and higher DA survival and less immune response |
| Brundin et al., 1986  | Rat fVM cells (1.2-1.5 \(\times\) 10^5) + rat fST cells (1.5-2 \(\times\) 10^5) or rat spinal cord cells (1.5-2 \(\times\) 10^5) 3 wk post-lesion | 6-OHDA (MFB) Rat (female)    | ▪ Co-grafted animals showed a tendency to improve behavioral effects (rotation test) |
|                       |                                                                                  |                               | ▪ Greater area of reinnervation after co-grafts                           |
|                       |                                                                                  |                               | ▪ Similar number of DA cells in co-grafted rats compared to rats grafted with fVM cells alone |
| Yurek et al., 1990    | Rat fVM cells (6-7.5 \(\times\) 10^5) + rat fST cells (6-7.5 \(\times\) 10^5) (mixed in the same cell suspension or grafted separately) Intrastratal | 6-OHDA Rat (male)             | ▪ Larger DA cell body, arborization and improved motor behavior (rotometer) after co-grafting |
| Authors                  | Cells/Sources                                      | Post-lesion Time | Treatment | Results                                                                                                                                 |
|--------------------------|----------------------------------------------------|------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------|
| Costantini et al., 1994  | Rat fVM cells (1 × 10^5) + rat fST cells (1 × 10^5) | 1 wk post-lesion | 6-OHDA (LV) Rat (3 days old) | - Co-transplants produced stronger behavioral effects and dense TH-positive patches within the grafts, without increasing DA survival |
| Emgard-Mattson et al., 1997 | Rat fVM + rat fST cells (lateral and medial ganglionic eminences) (7.9-12.7 × 10^4 total cells in the suspension) | 2-4 months post-lesion | 6-OHDA (MFB) Rat (female) | - Co-grafts containing lateral ganglionic cells showed patches of dense TH-positive fibers  
- No functional differences were observed after co-grafting (rotometer and staircase tests) |
| Sortwell et al., 1998    | Rat fVM cells (1.8 × 10^5) + rat fST cells (1.8 × 10^5) (mixed or grafted separately) | 4 wk post-lesion | 6-OHDA (MFB) Rat (male) | - Only rats that received co-grafts placed separately showed significant behavioral recovery and increased DA cell survival  
- Mixed co-grafts showed enhanced neurite branching and TH-positive rich patches |
| Sladek et al., 2008      | Monkey fVM cells (intranigral) + monkey fST cells (at different points rostrally to the fVM graft, following the nigrostriatal pathway) | 2-3 months post-lesion | MPTP Monkey | - Striatal grafts contained dense DA axons derived from the fVM graft (target-directed outgrowth) |
| Lee et al., 2003         | Human fVM + human fST (1 lateral ganglionic eminence) | 6-OHDA (LV) PD patient (male) | Improved motor function and increased L-DOPA uptake |
| Wilby et al., 1999       | Rat fVM cells (3.4 × 10^4 cells; intranigral) + GDNF-secreting SC line derived from rat sciatic nerve (2.5 × 10^5 cells; different deposits along the nigrostriatal pathway) | 3 wk post-lesion | 6-OHDA (MFB) Rat (female) | - Co-grafts improved DA survival and neurite outgrowth  
- No additional effects on motor functions |
| Rodriguez-Pallares et al., 2012 | Rat fVM cells (4.5 × 10^5) + carotid body cells (4.5 × 10^5) | 6 wk post-lesion | 6-OHDA (MFB) Rat (female) | - Significantly better motor performance (cylinder test) and improved DA survival and graft-derived DA innervation in rats that received co-grafts |
| Ostenfeld et al., 2002   | Rat fVM cells (2.5 × 10^6) + expanded NPCs obtained from rat fST tissue and modified to produce GDNF (4 × 10^5) | 3 wk post-lesion | 6-OHDA (MFB) Rat (female) | - Co-grafting increased DA survival  
- No significant effects on behavioral recovery |
| JingZhong et al., 2005   | Rat embryonic fibroblasts expressing TH + rat embryonic fibroblasts expressing GDNF (total number = 1 × 10^6) | 2 wk post-lesion | 6-OHDA (MFB) Rat (female) | - Only rats that received co-grafts showed stable and significant behavioral improvements (rotometer) and biochemical recovery (TH expression) |
| Deng et al., 2013        | Rat fVM cells (2.5 × 10^5) + rat NSCs overexpressing GDNF (2.5 × 10^5) | 2 wk post-lesion | 6-OHDA (MFB) Rat (male) | - Co-transplantation significantly reduced apomorphine-induced rotations |
| Experiment | NSCs/Cells Used | Treatment | Week(s) | Outcome |
|------------|-----------------|-----------|---------|---------|
| Perez-Bouza et al., 2017 | Cultured rat fVM cells (equivalent to ½ VM) + encapsulated mouse C2C12 myoblasts transfected to produce GDNF | 6-OHDA (MFB) Rat (female) | 2 wk post-lesion | Survival and differentiation of NSCs increased after co-grafting. Higher fiber outgrowth in co-grafted animals. Similar DA survival and graft volume. |
| Song et al., 2018 | Mouse or rat fVM-derived NSCs + mouse or rat VM- or cortex-derived astrocytes (ratio 2:1; total number = 4.5 × 10^5) | 6-OHDA (SN) Rat (female) | 13 wk post-lesion | Co-grafting with VM-derived astrocytes promoted DA differentiation of NPCs and increased fiber outgrowth. |
| Leveque et al., 2015 | Porcine fVM cells (3 × 10^5) + rat BM-MSCs | 6-OHDA (MFB) Rat (male) | 1 wk post-lesion | MSCs promoted long-term survival of DA neuroblasts and motor recovery. |
| Rodriguez-Pallares et al., 2021 | Rat fVM cells (5 × 10^5) + rat BM-MSCs (2.5 × 10^4 low dose) or 2 × 10^5 (high dose) | 6-OHDA (MFB) Rat (female) | 6 wk post-lesion | Increased survival of DA nigral neurons and striatal terminals after co-grafting fVM cells and low dose of MSCs. High dose of MSCs co-grafted with fVM cells decreased DA survival. |
| Shintani et al., 2007 | Rat fVM cells (8 × 10^4) + mouse CM-derived from BM-MSCs | 6-OHDA (MFB) Rat (male) | | Increased survival of grafted DA cells. |
| Clinical trial identifier NCT03684122 | Human UC-MSC-derived NSCs (8-12 × 10^6; intrathecal) + human UC-MSCs (8-12 × 10^6 intrathecal or 4-6 × 10^7 intravenous) | 6-OHDA (MFB) Rat (male) | PD patients | Clinical trial ongoing. |

6-OHDA: 6-Hydroxodopamine; BM-MSCs: bone marrow-derived mesenchymal stromal cells; CM: conditioned medium; DA: dopamine; DOPAC: 3,4-dihydroxyphenyl acetic acid; fST: fetal striatal; fVM: fetal ventral mesencephalic; GDNF: glial cell line-derived neurotrophic factor; L-DOPA: L-3,4-dihydroxyphenylalanine; LV: lateral ventricle; MFB: medial forebrain bundle; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NPCs: neural precursor cells; NSCs: neural stem cells; OECs: olfactory ensheathing cells; PD: Parkinson’s disease; SC: Schwann cells; SN: substantia nigra; TH: tyrosine hydroxylase; UC-MSCs: umbilical cord-derived mesenchymal stromal cells; wk: weeks.