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1980-2011: Parkinson's Disease and Advance in Stem Cell Research

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1. Introduction

Replenishing the depleted striatal dopamine stores with its immediate precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), to mimic dopamine-mediated neurotransmission still represents the gold standard for treating Parkinson's disease (PD). This pharmacological therapy offers immediate and effective symptomatic relief, especially at the early stages of the disease; it has, however, no influence on underlying neurodegenerative processes (Dass et al., 2006) that continue to evolve with time and are paralleled by a gradual loss of drug efficacy. As the disease progresses, steady adaptation, mostly continuous increase, of dopaminergic drug dosage is necessary, thereby favoring the emergence of considerable side effects, such as dyskinesia and psychiatric disturbances. The development of new treatments, or combination of treatments, able to relief motor symptoms and also delay or even halt the loss of dopaminergic neurons, has been and remains a fundamental issue for the development of innovative clinical strategies in PD. Transplantation of dopamine-secreting cells directly providing dopamine in the striatum, in particular, has been considered an adequate substitute to pharmacotherapy. However, although efficacy of this approach has now been asserted in numerous pre-clinical studies utilizing animal models of PD, positive outcomes in clinical trials involving PD patients have been very variable and rather modest, and have been plagued by graft-induced dyskinesias. New sources for cell replacement and particularly stem cells (including induced patient-derived cells) may now provide advantages for future clinical therapies (Wakeman et al., 2011).

This chapter will briefly introduce rodent and nonhuman primate PD-like models commonly used in pre-clinical studies, which represent a fundamental platform for the pre-clinical evaluation of innovative interventions. We will then evidence the progresses accomplished since the first intracerebral transplantation of fetal neural tissue in PD patients describing the subsequent novel discoveries for the application of stem cell to pre-clinical PD models, and give an overview of ongoing cell-based therapeutic strategies. Thereafter, multiple issues connected to stem transplantation to efficiently contrast adverse effects of increased age will be reviewed including decrease of apoptosis related to tissue degeneration, requirement of correct graft integration in the host vascular and neural

circuits, reduction of diffuse inflammatory response/oxidative stress and correct release of key growth factors. In addition we will discuss the emergence of novel biotechnologies that will, most likely, help unravel the complex interrelationship between transplanted stem cells and the host environment and will favor the development of novel therapeutic procedures readily applicable in PD patients.

2. Animal models: A necessary pre-clinical tool for the development of innovative cellular therapy in PD

Animal models represent a fundamental step in the attempt to elucidate gene-environment interactions and to define pathogenic mechanisms involved in the aetiology and progression of the neurodegenerative diseases. Most of the current knowledge on pathophysiology of PD originates from studies conducted on animal models of the disease, since animals and humans share several anatomical features (as shown in Figure 1). In addition, they represent the first essential pre-clinical platform for the evaluation of any targeted therapeutic intervention. Notably, subsequent clinical trials in small human cohorts remain essential for the development of efficient therapies able also to alleviate disability related non-motor symptoms (Meissner et al., 2011) which are currently underestimated in animal models (Dunnett and Lelos, 2010).

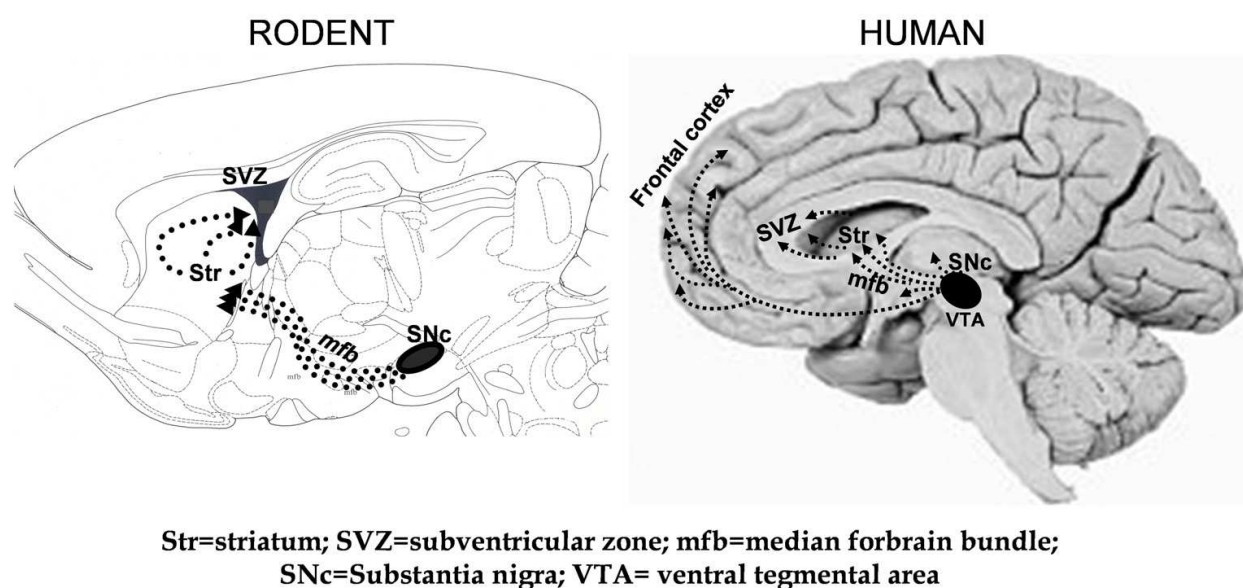


Fig. 1. Anatomical comparison between mouse and human brains

The comparison between rodent (A) and human brain (B) enlightens their anatomical similarities and physiology. The connections between striatum, SNc, and cerebral cortex in the human brain are indicated by dotted black lines and may correlate the simultaneous degeneration of these areas during disease onset and progression. Moreover, dopaminergic innervations of the striatum/SVZ (black dotted lines) could also explain reduction of adult brain neurogenesis both in PD patients and animal models.

PD models have been classically based on the administration of neurotoxins able to replicate some of the pathological and phenotypic features of the human disease both in rodents and

primates. Toxins can be given systemically or intra-cerebrally, depending on the type of toxin used and animal specie involved, and mimic the selective degeneration of nigrostriatal neurons characteristic of the human disorder.

The classical systemic model is based on the injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxin that selectively affects dopaminergic neurons and first recognized in the mid-1980's as the cause of marked parkinsonism in young drug users of Northern California (Langston et al., 1983). MPTP crosses the blood brain barrier and is transformed in its active metabolite, 1-methyl-4-phenylpyridinium ion (MPP⁺) that is then actively taken up by dopaminergic neurons of the substantia nigra pars compacta (SNc). Systemic administration of MPTP to nonhuman primates induces a parkinsonian phenotype closely resembling the human pathology. MPTP-treated monkeys have an excellent anti-symptomatic response to dopaminergic drug treatment and develop motor complications linked to long term L-DOPA therapy (Kim et al., 2009). Concordantly, several pharmacological drugs currently applied to treated PD patients (i.e. dopamine agonists, amantadine, etc..) have been developed in this MPTP model (Fox et al., 2006). Alternative cell replacement strategies using various cell sources have been successfully performed indicating the technical feasibility of the model for future studies (Redmond et al., 2010; Serra et al., 2008). The large related costs and the difficulty to reliably standardize acute toxin administration to replicate most of the underlying mechanisms of a chronic progressive disorder form still represent major drawbacks and limit the use of this PD model in large scale studies (Fox and Brotchie, 2010). MPTP can also be systemically administered to mice but not rat, which are resistant, and several different experimental paradigms have been developed and used over time.

The prototypical intracerebral model is based on the local injection of 6-hydroxydopamine (6-OHDA) and was the first PD animal model ever generated (Ungerstedt, 1968). 6-OHDA is a hydroxylated analogue of dopamine and, similarly to MPTP, is actively taken up by dopaminergic neurons. The neurotoxin can be injected in the SNc, or into the medial forebrain bundle (mfb) that conveys efferent fibers from the nigral cell bodies to the striatum (as shown in Figure 1) and causes massive and rapid anterograde degeneration of the nigrostriatal pathway. This procedure induces large nigral cell loss and striatal dopamine depletion (90-100%). The neurotoxin can also be injected into the striatum; in this case rapid damage to striatal dopaminergic terminals is observed followed by a progressive loss of SNc neurons (50-70% neuronal loss), which are secondarily affected through a "dying back" mechanism. This procedure has a slower time course compared to the intra-mfb injection and provides a progressive model of nigrostriatal degeneration, more similar to the gradual evolution of the neurodegenerative process of human PD. Importantly, injection of 6-OHDA is commonly carried out unilaterally, with the contralateral hemisphere serving as control, because of the high mortality rate associated with bilateral injection. The rat 6-OHDA model is commonly used in neuroprotective studies, both involving administration of novel pharmaceutical compounds or cell transplantation because it is i) cost-effective, ii) highly reproducible and iii) opened to articulate behavioural analyses (Redmond et al., 2010; Serra et al., 2008).

Numerous transgenic mouse models, that reproduce monogenic mutations observed in familiar forms of PD, have also been developed over the years. These models have not been discussed in this chapter as they typically display very low degree or even no nigrostriatal degeneration (for review see (Dawson et al., 2010)) and are not commonly used in stem cell transplantation experiments.

3. Neural tissue transplantation

In 1987, the first clinical trials involving transplantation of human fetal mesencephalic tissues or xenotransplantation of fetal pig neural cells in humans were performed with the clear scope of replacing dopaminergic neurons lost during PD progression. Since then and overall, contradictory results have been observed, even among patient groups treated within the same centers (Bjorklund et al., 2003). Along with the observed poor graft survival (around 10%; (Hagell and Brundin, 2001), a substantial subset of patients (15-56%) developed dyskinesias (Freed et al., 2001; Hagell and Brundin, 2001; Olanow et al., 2003), while the presence of Lewy bodies in long-term implants, recently reported, suggests the possibility of a *host-to-graft* disease propagation (Kordower et al., 2008; Li et al., 2008; Mendez et al., 2008). Functional improvements, represented by reduction of symptoms (30%–40% improvement of the unified Parkinson's disease rating scale, motor score in the drug-free phase) have been clearly observed (Hagell and Brundin, 2001) even in the long term (Mendez et al., 2008; Piccini et al., 1999). Positive outcomes were dampened by enhanced microglial activation and disruption of blood brain barrier linked to surgical procedures (Olanow et al., 2003). Failures were also related to the scarcity, as well as heterogeneous composition of the donor tissue itself (Carlsson et al., 2009; Freed et al., 2001). Nonetheless, these first trials supported the feasibility of transplantation procedures as an alternative therapeutic approach in PD (Brundin et al., 2010; Olanow et al., 2003). Moreover, these first trials have enlightened critical parameters mandatory for successful transplantations including: a) purity of cell preparation; b) correct localization of the graft in the host brain c) preference for reduced age of donor/host cells (whenever possible), d) limited extension of brain injury at the time of transplantation (early pathological phases), and e) appropriate time of grafting (in relation to disease onset) to maximize survival of endogenous dopaminergic neurons (Lindvall and Kokaia, 2009). Altogether, these observations have encouraged the search for alternative cell sources that need to be efficient, safe, and ethically acceptable (additional details on this debated/controversial topic can be found in (Kimmelman et al., 2009)).

4. Stem cell therapy

The scientific progresses in biological and cellular technologies have allowed a better conception of the mechanisms involved in cell development, and in particular of factors/conditions ruling Stem Cells (SCs) proliferation and differentiation. Essentially, SCs are undifferentiated multipotent cells capable of both self-renewal and generation of several differentiated functional cell types to preserve tissue homeostasis throughout the entire life span of an organism. Multiple properties of SCs, including their the ability to potentially generate an unlimited number of dopaminergic neurons under physiological conditions, make them attractive candidates for regenerative therapy (Dass et al., 2006).

Therefore, SCs have been increasingly recognized as a valuable replacement and/or supporting tool for PD wherein a well-characterized cell type is mainly affected. Cell therapy may be performed using either autologous (ideal from an immunologic perspective) or allogeneic tissue-specific differentiated cells. Transplantation of healthy SCs that have been collected, expanded and eventually pre-differentiated *in vitro* have been originally proposed as a feasible appealing neural-replacement strategy. To date, several fetal and adult SC lineages have been directly differentiated into multiple cellular types, including neural cells and dopaminergic phenotypes. These naïve SCs, or their induced neuronal

progeny, have been successfully transplanted in animal models of PD granting significant behavioral improvements. Ideally, however, new therapies should not only aim at replenishing the depleted dopamine store, but should also allow rescue of neuronal terminals and soma both in striatum and SNc.

Innovative therapeutic strategy should also take advantage and enhance the plastic property of the adult Central Nervous System (CNS) to regenerate affected brain areas through the activation of endogenous neurogenesis following cell transplantation. To reach these targets, other known intrinsic properties of SCs have already been exploited. Indeed, the potential of SCs to restore injured tissues is not only related to their direct differentiation but also to their capacity to produce and release trophic factors that may in turn inhibit apoptosis, promote angiogenesis and even direct stimulation of host regeneration (Lindvall and Kokaia, 2009; Lindvall and Kokaia, 2010). Neuroprotection can also be enhanced by transplanting SCs engineered to express either tyrosine hydroxylase (TH), the rate-limiting enzyme of dopamine synthesis, or neurotrophic factors, such as glial cell-line derived neurotrophic factor (GDNF), the most potent survival factor for degenerating dopaminergic neurons. Grafting of engineered SCs in this case provides a substantial reservoir allowing the unlimited supply of the required substance without the requirement of invasive injection pumps, as detailed below. Several SC types have already been transplanted in PD animal models yielding interesting but variable results (Wakeman et al., 2011).

SCs can be efficiently derived from early stage embryos (pluripotent SCs with unlimited potential to differentiate) or from committed resident tissues (multipotent SCs with restricted potential to differentiate). Interestingly almost all organs arising from endodermal, mesodermal and ectodermal germ layers can originate both fetal and adult SCs (i.e. amniotic/cord blood and tissue derived SCs). Regardless of their origin SCs could physiologically repair damaged tissues after intense injuries also promoting angiogenesis and neurogenesis processes, essential for CNS development and regeneration (Lindvall and Kokaia, 2010).

4.1 Embryonic stem cells

Embryonic Stem cells (ES) are derived from the inner cell mass of pre-implantation embryos and are a source of pluripotent cells, as they are able to differentiate into all adult cell types. Once established, the pluripotent ES cells can be maintained under defined culture conditions, but can also be induced to terminally differentiate into a specific lineage (Bibikova et al., 2008). ES cells may potentially give rise to an infinite number of dopaminergic neurons that may be subsequently transplanted in depleted brain areas either in animal models of PD or even in patients (Lindvall and Kokaia, 2009). A particular emphasis has been posted on the validation of reliable methods for differentiation of ES cells towards midbrain dopaminergic neurons with a high survival index following transplantation (Hwang et al., 2010). Several protocols, characterized by presence of different feeder cell layers (i.e. bone marrow stromal cells, (Perrier et al., 2004) or astrocytes (Roy et al., 2006)) coupled to morphogen/growth factor exposition, have been developed. Transplantation of these *in vitro*-differentiated cells has produced variable results and often gave rise to tissue overgrowth with formation of neuroepithelial tumors, probably linked to the presence of residual immature cells in the original grafts. To overcome uncontrolled proliferation within transplants, cell-sorting protocols have been applied to specifically isolate pure populations of ES-derived dopaminergic neurons. These procedures, however, selectively impaired neuron survival indicating that fundamental factors were lost in the negative fraction (Friling et al., 2009).

Recently, epigenetic manipulation to force dopaminergic gene expression has been also exploited (Andersson et al., 2006). Following transplantation in parkinsonian rats, these differentiated cells integrated in the brain of the animals and significantly improved PD-related behavioral stereotypies (Yang et al., 2010). Application of this methodology to clinical practice, however, remains unrealistic until well-standardized, tumor-free samples will be available. Additional protocols for induction of dopaminergic phenotypes in ES cells have been recently developed (Chambers et al., 2009; Cooper et al., 2010), but functional efficacy of these cells has not been tested in PD animal models yet. Moreover, their use is still limited by our scarce knowledge of the development and specification of midbrain dopaminergic neurons (Pruszek and Isacson, 2009). Altogether, all experimental studies performed so far, demonstrate that ES-derived dopaminergic neurons are still unable to efficiently survive in and innervate lesioned brain areas in animal models of PD without inducing the formation of tumors (Arenas, 2010). In addition, ES cells frequently carry aberrant chromosome content in relation to growth advantage (Meisner and Johnson, 2008). Finally, the therapeutic application of ES cells will necessarily require both animal cell- and serum-free conditions (Klimanskaya et al., 2005), still substantially limiting their standardized application in clinic (Gruen and Grabel, 2006).

4.2 Induced pluripotent SCs

Recently, induced Pluripotent SCs (iPS) have been derived from primary fibroblast cultures obtained from cutaneous biopsies of patients affected by neurodegenerative diseases (Kriks and Studer, 2009; Lindvall and Kokaia, 2009). This complex reprogramming sequence was performed by exogenous expression of specific transcription factors that allowed a cellular switch from an epigenome of reduced potency to one of pluripotency (Kiskinis and Eggan, 2010). The resulting iPS cells could then be differentiated into autologous, patient-specific non-mitotic cells, such dopaminergic neurons and glial cells, normally present only in the CNS, and generally only available post-mortem.

iPS cells present several advantages when compared to ES cells: 1) their possible autologous derivation (Park et al., 2008b), 2) the consequent lack of mandatory immunosuppressant therapy following transplantation, and 3) the absence of ethical concerns related to embryo disruption (Arenas, 2010). These derived and/or differentiated cells can be used as donor cells in transplantation paradigms and represent a valuable tool to dissect intrinsic pathological mechanisms or test new pharmacological approaches in samples not readily available from live patients (Abeliovich and Doege, 2009; Gunaseeli et al., 2011; Xu et al., 2010a). However, the use of oncogenes or retrovirus in the current iPS cell establishment protocol raises considerable safety concerns (Pasi et al., 2011). Indeed, iPS progenies show high propensity to form teratomas considerably restricting their potential use in cell therapy (Miura et al., 2009). Heterogeneity of iPS cell composition with variable levels of transgene expression overtime suggests a prudent approach for iPS application to clinical trials (Kiskinis and Eggan, 2010). Recently, alternative protocols that allow direct fibroblast reprogramming towards neurons without generation of pluripotent cells have been developed (Vierbuchen et al., 2010). An additional notable potential risk of autologous therapeutic reprogramming is linked to the possibility that unknown genetic factors, involved in the patient's disease, could also potentially lead to disease-related alterations of the transplanted cells in the long term (Hwang et al., 2010). Transplantation of committed neural cells selected from differentiated PD patient-derived iPS cells has been tested in a lesional rodent model of PD with some overall beneficial effects. Transplanted cells

integrated into the striatum of parkinsonian rats and improved behavioral deficits for up to 8 weeks, although no noticeable dopaminergic innervation from grafted cells to the surrounding striatum was observed (Wernig et al., 2008). Recently, Hargus et al, showed that iPS-derived dopaminergic neurons can be implanted and survive, without signs of neurodegeneration or tumor formation, both in healthy and 6-OHDA lesioned rats (Hargus et al., 2010). Although the grafted cells sent proper projections to close and remote target areas, acquisition of the appropriate regional identity is still argued. A significant behavioral improvement related to high survival of the transplanted dopaminergic neurons was also reported in simple, but not in complex motor functions, that rely on functional connections between grafted and host cells. Therefore, whether these preliminary results can be successfully translated into human clinical studies still awaits more experimental data (Hanna et al., 2010). Additional long-term studies will be necessary to recreate the correct pathophysiological conditions before validation of this model as an alternative cell-based therapy in PD (Kiskinis and Eggan, 2010). It has been hypothesized that an effective therapeutic effect following transplantation requires the survival of at least 10^5 electrophysiologically active dopaminergic cells, appropriately contacting and reinnervating striatum, without tumor formation (Arenas, 2010). Nevertheless, iPS cells could still be exploited for drug screening or as disease model to unravel pathological cascades in PD (Xu et al., 2010a). An important draw back in the clinical application of iPS cells also resides in the elevated production costs of personalized iPS. The establishment of centralized iPS cell bank(s) has been proposed to insure that fibroblast-derived dopaminergic neurons for transplantation are obtained following the Good Manufacturing Practice (GMP) guidelines for clinical trial materials.

4.3 Patient-derived Neural SCs

An innovative cellular approach is based on patient-derived neural stem cells (NSC) obtained from biopsies of their olfactory mucosa biopsies. This procedure allows the derivation of large quantities of NSC that can be grown *in vitro* as floating differentiable neurospheres. The cells bear significant pathological, disease-specific alterations in gene and protein expression, as well as cell function, such as dysregulated mitochondrial function, oxidative stress and xenobiotic metabolism (Matigian et al., 2010). Direct exploitation of these patient-derived neural cells will help obtain new insights in specific candidate genes and cell pathways for future studies of brain disease. These SCs could partially overcome the lack of appropriate animal models, faithfully recapitulating all of the clinical and pathological phenotypes of the disease, to study the mechanisms underlying PD as well as to develop translational drug development (Schule et al., 2009). In addition, these cells have a considerable advantage over ES and iPS cells, as they do not require reprogramming, and represent an important tool, with a considerable translational impact to all complex diseases. Moreover, biopsies easily obtained from neural tissues could supply new biomarkers for monitoring disease progression in PD patients. Development of such biomarkers represents a necessary step for the accomplishment essential for quality research and clinical trials (Lebouvier Thibaud et al., 2010). Derivation of patient NSC encompasses all the specific gene-environment interactions which appear fundamental along ageing process in sporadic neurological as well as psychiatric disorders (Matigian et al., 2010). Patient derived SCs are particularly intriguing for their potential in cell therapy and regenerative medicine: they may provide novel insights for the development of therapeutic strategies, aiming to contrast the neurodegenerative processes of PD. The discovery of the

specific molecules involved in these biological events could also shed light on new pharmacological disease-modifying treatments and novel potential targets, readily applicable to patients (Schule et al., 2009).

Anyway, a cautionary approach is required, since this invasive methodology still requires development of standardized, validated protocols able to reach a structure (olfactory mucosa) not accessible to routine biopsies (Parkkinen et al., 2009)].

4.4 Multipotent adult stem cells

Multipotent SCs have been identified within specific niches in most adult tissues including bone marrow, muscle, brain, heart and liver. Adult SCs that comprise fetal, amniotic, umbilical cord blood, placental, as well as tissue derived SCs (i.e. hematopoietic, neural, mesenchymal, skin SCs) are less abundant and proliferative, and possess limited potential to differentiate compared to ES cells. A key added value of adult SCs, however, is their potential use in autologous therapies, in which cells can be harvested and used within the same patient, thus avoiding the ethical concerns and risks linked to ES cells (Fricker-Gates and Gates, 2010). The ideal procedure involves isolation of SCs from tissues and their preservation in standardized stocks at centralized unit banks for long term storage and subsequent transplantation into patients upon request (Arenas, 2010) (see Figure 2). In this section we will summarize the actual state of the art and deadlocks regarding three main SC lineages: hematopoietic (HSC), mesenchymal (MSC) and neural (NSC).

Bone marrow resident HSC and MSC constitute two important cell sources for pre-clinical transplantation. HSC can be easily derived from autologous/allogeneic bone marrow or peripheral blood, and are routinely used in transplantation procedures for the treatment of several immuno-deficient/autoimmune diseases, as well as hematopoietic disorders, to reconstitute peripheral cell lineages (i.e. leukocytes, erythrocytes, etc). Recently, transplantation of HSC, engineered to release TH, has been reported to produce significant therapeutic effects in PD rats (Zhang et al., 2008).

A large body of data on the application of MSC in cell therapy can be found in literature; MSC are non-hematopoietic, multipotent cells which arise from the stromal structures of the bone marrow and are preserved in adults (Picinich et al., 2007). MSC can generate mature endothelial cells and several mesenchymal cell lineages including osteoblasts, chondrocytes, adipocytes and myoblasts (Liu et al., 2009). Several publications report efficient and multi-disciplinary protocols for their differentiation, *in vitro*, towards dopaminergic neurons (Heinrich et al., 2009; Kitada and Dezawa, 2009) even including the use of lentiviral vectors to induce TH expression (Barzilay et al., 2009). Positive outcomes in acute hypoxic-ischemic damages have been obtained utilizing MSC isolated from several stem sources, such as human placenta and amniotic fluid, either naïve (Cipriani et al., 2007) or following neural differentiation (Park et al., 2011). Positive results, such as stability and physiology of the correct phenotype *in vitro* (Thomas et al., 2011) and *in vivo* after transplantation of MSC in animal models of PD (Shetty et al., 2009), as well as in PD patients (Venkataramana et al., 2010) have been reported. The long-term fate of grafted cells is still, however, matter of debate (Schwarz and Storch, 2010; Schwarz and Schwarz, 2011) and application of cell therapy to a chronic degenerative disease like PD appears rather complex. Successful outcomes of transplantation can be influenced by multiple factors largely dependent on the source and type of SCs adopted. For example, it has been reported that neural differentiation of MSC is required before intrastriatal transplantation in PD rats to observe a graft-dependent improvement of motor deficits (Levy et al., 2008). Transplantation of naïve

human umbilical vein-derived dopaminergic-like cell in a rat model of PD did not improve motor dysfunction, and required administration of a neurotrophin, nerve growth factor, to induce substantial recovery (Li et al., 2010a). Lineage negative cells from umbilical cord blood efficiently gave rise to neuronal cells and oligodendrocytes *in vitro* (Chua et al., 2009) while lineage specific (cKit+) amniotic-derived SCs fail to acquire a dopaminergic phenotype after epigenetic stimuli both *in vitro* and in an animal model of PD (Donaldson et al., 2009). Concordantly, upon neuronal induction bone marrow-derived MSC down-regulate markers of other lineages, but fail to differentiate into functional neurons (Thomas et al., 2011). The functional positive effects exerted by transplanted MSC in PD animal models, are still controversial on the basis of technical criticisms, strength of trial design or inconsistent experimental approaches (Meyer et al., 2010). MSC have a significant protective effect against dopaminergic cell loss both *in vitro* and *in vivo* (Park et al., 2008a), but whether this results from true dopaminergic neuron replacement and how the cells actually induced functional improvement are still far from being clarified (White, 2011). Thus, before MSC can be considered a reliable source for clinical replacement of dopaminergic cells, their ability to transdifferentiate terminally towards a neuronal lineage needs to be resolved and their mechanism of action following transplantation needs to be elucidated (Schwarz and Storch, 2010).

Another promising source of SC is represented by NSC, that can be derived from various source including the subventricular zone (SVZ), ES, umbilical cord blood, MSC, fetal brain as well as spinal cord, and grown in suspension as floating clusters (neurospheres) (Meyer et al., 2010). NSC can restore functions lost during ageing, and both migrate towards and repair neurological damages, exerting positive influence on the surrounding cells, including dysfunctional neurons (Ourednik et al., 2002). Autologous transplantation of *in vitro*-expanded cortical and subcortical tissue samples, obtained from a PD patient during a neurosurgical procedure, produced long lasting motor improvements (Lévesque et al., 2009). Interestingly, fetal and adult NSC possess comparable intrinsic therapeutic potential in terms of cell survival, integration and functional outcomes in a rat model of PD (Muraoka et al., 2008). However, albeit feasible, harvesting samples from patient remains an invasive procedure and is difficult to translate into a routine therapy. NSC do not give rise to dopaminergic neurons under physiological conditions, but several protocols have been optimized for their forced differentiation towards this lineage. Mimicking the procedures for dopaminergic differentiation from ES cells, a group has reported the differentiation of immature NSC into forebrain, but not midbrain (area A9), dopaminergic cells (Papanikolaou et al., 2008), while forced expression of Nurr1, a transcriptional factor specific for midbrain dopamine neuron development, induced dopaminergic neuron phenotype in NSC isolated both from SVZ and the white matter (Shim et al., 2007). The appearance of specific neuronal subtypes is not solely a direct consequence of external cues or the expression of neurotrophins but likely depends on the integrated temporal sequence of multiple factors that finally results in the correct neuronal phenotype. Regionalization and specification of the midbrain territory rely on a defined pattern of transcription factor expression and secretion of soluble molecules within the neuroectoderm in physiological conditions. This pattern is a composite process difficult to correctly recapitulate *in vitro* and has been only partially unraveled (Fricker-Gates and Gates, 2010). Interestingly, transplantation of NSC derived from MSC, using a complex protocol based on TH transfection and culture in media for differentiation, in 6-OHDA lesioned rats has been recently reported. Cell grafting induced significant behavioral improvements that were associated with partial preservation

of dopamine content (Zou et al., 2010). A similar approach was applied to MPTP-lesioned parkinsonian rhesus monkeys; transplantation of TH- transfected bone marrow cells in the caudate nucleus and SNc improved both PD-related alterations in glucose metabolism and dopamine transport with an overall recovery of behavioral symptoms (Xu et al., 2010b). Similarly, allogeneic NSC modified to stably express and release the neurotrophic factor Neurotrophin-3 (NT-3), displayed enhanced dopaminergic neuron differentiation as well as migration distance, and induced the reinnervation in the neural circuitry coupled to functional recovery upon transplantation in 6-OHDA-treated rats (Gu et al., 2009). Recently, Murrell and colleagues proposed that dopaminergic neurons may be generated directly from adult olfactory SC of PD patients, similarly to Matigian et al (Matigian et al., 2010): in this paper the authors further demonstrated that differentiation of neural progenitor cells in dopaminergic-like neurons was able to correct behavioral asymmetry in the rat model of PD (Murrell et al., 2008).

Albeit these overall positive data, additional long term trials on the safety, efficacy, as well as further understanding of the biological mechanisms activated by graft procedures still need to be accomplished. So far, real functional integration between ectopically grafted SC-derived dopaminergic neurons in the denervated striatum has been demonstrated only in organotypic cultures of wild type mouse striatum (Tonnesen et al., 2011). Therefore, studies aimed at the characterization of the molecular basis of the integration in/differentiation of (genetically modified) NSC, and their progeny, within the dopaminergic network deserve further extensive development. Finally, the invasive intracerebral procedure required for the isolation of NSC as a possible SC source in the treatment of neurodegenerative diseases still remains a major draw back for their clinical application.

It is also important to notice that all the three SC lineages (HSC, MSC and NSC) can be obtained from bank-stored umbilical cord blood and amniotic/placenta cells, while only HSC and MSC can be easily isolated from autologous peripheral blood, thus amplifying the potential SC pool for clinical or experimental settings without ethical concerns (Figure 2).

5. Stem Cell & Neuroinflammation

Recent discoveries regarding the role of the immune system in brain damage coupled to the development of new technologies to manipulate the immune response make immunotherapies an attractive target to treat neurological diseases (Tansey and Goldberg, 2010). In the past decade, neuroinflammation has emerged as an important substrate for PD (Brochard et al., 2009). Several epidemiologic studies have reported an inverse correlation between the chronic assumption of non-steroidal anti-inflammatory drugs and the risk of developing PD (Chen et al., 2003). Unrestrained widespread neuroinflammation emerges during the early phases of the neurodegenerative process both in PD patients and in animal models of the disease (Whitton, 2010) and significant evidence demonstrates that neuroinflammatory processes participate in PD pathophysiology. Gliosis and lymphocyte infiltration associated with production of soluble factors – potentially protective or toxic – are consistently reported in parkinsonian animals and PD patients (McGeer et al., 1988; McGeer and McGeer, 2004; McGeer and McGeer, 2008). Most studies in animal models of PD have demonstrated that efficient neuroprotective strategies that decrease nigrostriatal degeneration also consistently reduce associated neuroinflammatory processes, and *vice-versa*, underlying the fundamental link between neuroinflammation and neurodegeneration. Recent data have also supported the idea that a reduction in the levels of anti-inflammatory

factors itself can further enhance vulnerability of dopaminergic neurons to apoptosis in a neurodegenerative environment (Barnum and Tansey, 2010; Lu et al., 2010; Maguire-Zeiss and Federoff, 2010). Furthermore, it has been recently suggested that pro-inflammatory cytokines exert a negative impact on neuronal differentiation, while anti-inflammatory cytokines facilitate neurogenesis (Mathieu et al., 2010) and neuronal migration towards appropriate targets (Das and Basu, 2008). These data clearly indicate that pro- and anti-inflammatory responses must be strictly balanced to prevent the potential detrimental effects of prolonged or unregulated inflammation on vulnerable neuronal populations (Lee and Park, 2009). It has been shown that outcome of the transplantation of ES-derived TH-positive cells in an MPTP mouse model of PD is strictly dependent on the concomitant administration immunosuppressive treatment (Toriumi et al., 2009) that significantly improved survival and integration of grafted SC overtime.

Noteworthy, inflammation, which has long been considered as thoroughly disastrous for brain repair, is now known to produce some positive effects on stem/progenitor cell recruitment/survival by growth factor signalling and the secretion of chemoattractant cytokines (Cayre et al., 2009; Mathieu et al., 2010). Conversely, inflammatory mediators, such as nitric oxide (NO) and reactive oxygen species (ROS), can contribute to neurodegeneration by triggering aberrant protein modifications with consequent misfolding and loss of function (Vicente Miranda and Outeiro, 2010). Application of MSC, a particular SC lineage described above (section 4.4), that knowingly possess significant inherent immunomodulatory properties, opens new perspective for cell transplantation in PD. MSC can interactively act on their environment through the local/distal release of trophic factors, as well as on the activation of immune response by means of cell contact-dependent mechanism and modulation of noxious inflammatory components (Lee and Park, 2009). MSC were proven to effectively protect dopaminergic neurons from lipopolysaccharide (LPS)-induced neurotoxicity, both *in vitro* and *in vivo*, via anti-inflammatory mechanisms involving the modulation of microglial activation (Kim et al., 2009). Microglia, in turn are responsible for the correct phagocytic clearance following injury, thus facilitating the reorganization of neuronal circuits and triggering repair (Neumann et al., 2009). Notably, aside from immunomodulation, the complex network of biological mechanisms activated by MSC transplantation includes their homing to the SNc, substitution of dopaminergic neurons, modulation of apoptosis and modification of ubiquitin-proteasome function. Concordantly, at the moment, MSC constitute the most attractive and autologous candidate disease modifying strategy for PD and other neurodegenerative disorders (Karussis et al., 2008).

6. Neurorepair/Neurogenesis

The nigrostriatal network is highly organized and finely regulated in relation to specific functions and circumstances. As a consequence, restoring lost dopaminergic neurons does not necessarily coincide with correct reconstruction the pathway (Obeso et al., 2008). Partial maintenance of neuron survival and function in the SNc within the neurodegenerative environment, following transplantation of SCs could, *per se*, potentially translate in significant therapeutic outcomes. Substantial neuroprotective effects against dopaminergic depletion have been observed, for example, after transplantations of naïve, undifferentiated SCs such as adult adipose-derived adult stromal cells (McCoy et al., 2008), human NSC (Yasuhara et al., 2006) or human MSC (Blandini et al., 2010) in 6-OHDA lesioned rats.

Similarly, neuroprotection was evident following grafting of human MSC in an animal model of progressive parkinsonism (Park et al., 2010; Park et al., 2008a). In an interesting approach, transplantation of genetically engineered NSC, in animal models of brain tumor or injury, could served as incessant sources of secreted therapeutic agents (neuroprotective or tumoricidal) playing the role of biological minipumps (Chen et al., 2007). This procedure could readily be applicable to neurodegenerative diseases, including PD. As already described for neuroinflammation, the complex interactions between grafted SCs and endogenous surrounding cells can reciprocally influence outcome of transplantation both through direct interconnections (adherent junctions) or long distance mediations (release of soluble factors) (Boucherie and Hermans, 2009). In Amyotrophic Lateral Sclerosis for example, non-neuronal neighboring cells, including astrocytes, can drastically enhance neuronal survival (Nagai et al., 2007). Concordantly, in PD, glial cells play a critical role in homeostatic mechanisms that promote neuronal survival through release of an array of pro- and anti-inflammatory cytokines, anti-oxidants and neurotrophic factors within the microenvironment of the brain (L' Episcopo et al., 2010). Interestingly, grafting of MSC differentiated towards astrocyte-like phenotypes resulted in relevant improvements of motor impairment in 6-OHDA lesioned rats in the absence of dopaminergic differentiation (Bahat-Stroomza et al., 2009). Similarly, naïve MSC transplanted in the striatum of 6-OHDA lesioned animals acquired a glial-like phenotype and significantly reduced the toxin-induced neurodegeneration (Blandini et al., 2010).

Recent innovative approaches also include the use viral vectors to induce selected SC to produce/release specific neurotrophins possibly active in repairing/rescuing the degenerating nigrostriatal system. New protocols for efficient transduction of MSC allowing enhanced delivery of GDNF have been developed. Transplantation of the transduced cells in experimental PD resulted in the preservation of striatal TH immunoreactivity around the graft (Moloney et al., 2010). Similarly, GDNF- and Brain Derived Neurotrophic Factor (BDNF)-secreting MSC transplanted in 6-OHDA lesion rats improved behavioral deficits, typically detected in these animals (Sadan et al., 2009). Human neural progenitor cells that had been genetically modified to release GDNF, readily survived without tumor formation, following the intrastriatal transplantation into the brain of aged monkeys (Behrstock et al., 2006). A comparative study with non human primate has evidenced that the striato-nigral axon-transport is also compromised in advanced PD patient potentially limiting the regular retrograde transport of factors towards affected neuronal bodies in the SNc (Bartus et al., 2011). These therapeutic strategies may, therefore, be applicable mainly to patients at an early stage of the disease when part of the nigrostriatal network is still spared and may be rescued. Different clinical approaches may be required as disease proceeds with the wide loss of dopaminergic neurons (Rascol, 2009).

Donor cells, to physiologically repair damaged neural circuitry using SC transplantation, must be able to survive in sufficient number, to differentiate into the appropriate cell type and to adequately support the host brain environment. To optimize functional recovery and minimize side effects, grafted SCs should be able to functionally integrate in and be regulated by the host brain. Outcome of transplantation may be directly affected by time of grafting and cell number (Darsalia et al., 2011). Correlation between cell amount and therapeutic effects has, for example, been demonstrated for naïve MSC that dose-dependently and regionally sustained the survival of striatal/nigral dopaminergic terminals and enhanced neurogenesis, following intrastriatal transplantation in parkinsonian rats (Blandini et al., 2010; Cova et al., 2010). Among the pathogenetic mechanisms involved in

PD a role of reduced neurogenesis has been suggested (Geraerts et al., 2007). The SVZ, one of the two neurogenic zones region located in the lateral wall of the ventricles that maintains the largest pool of proliferating cells in the mature mammalian CNS, receives organized projections from the SNc. These efferent projections can influence precursor cell proliferation in both adult animal (Baker et al., 2004; O'Keeffe et al., 2009a) and primate models (Freundlieb et al., 2006), probably through dopamine-induced release of Epidermal Growth Factor in the SVZ (O'Keeffe et al., 2009b). Dopaminergic denervation within SVZ causes a reduced rate of neural precursor mitosis and abridged neuronal maturation in the long term, a phenomenon common among PD patients (Hoglinger et al., 2004) and toxin-induced animal models of PD (Aponso et al., 2008; He et al., 2006; He et al., 2008; Winner et al., 2009; Winner et al., 2006).

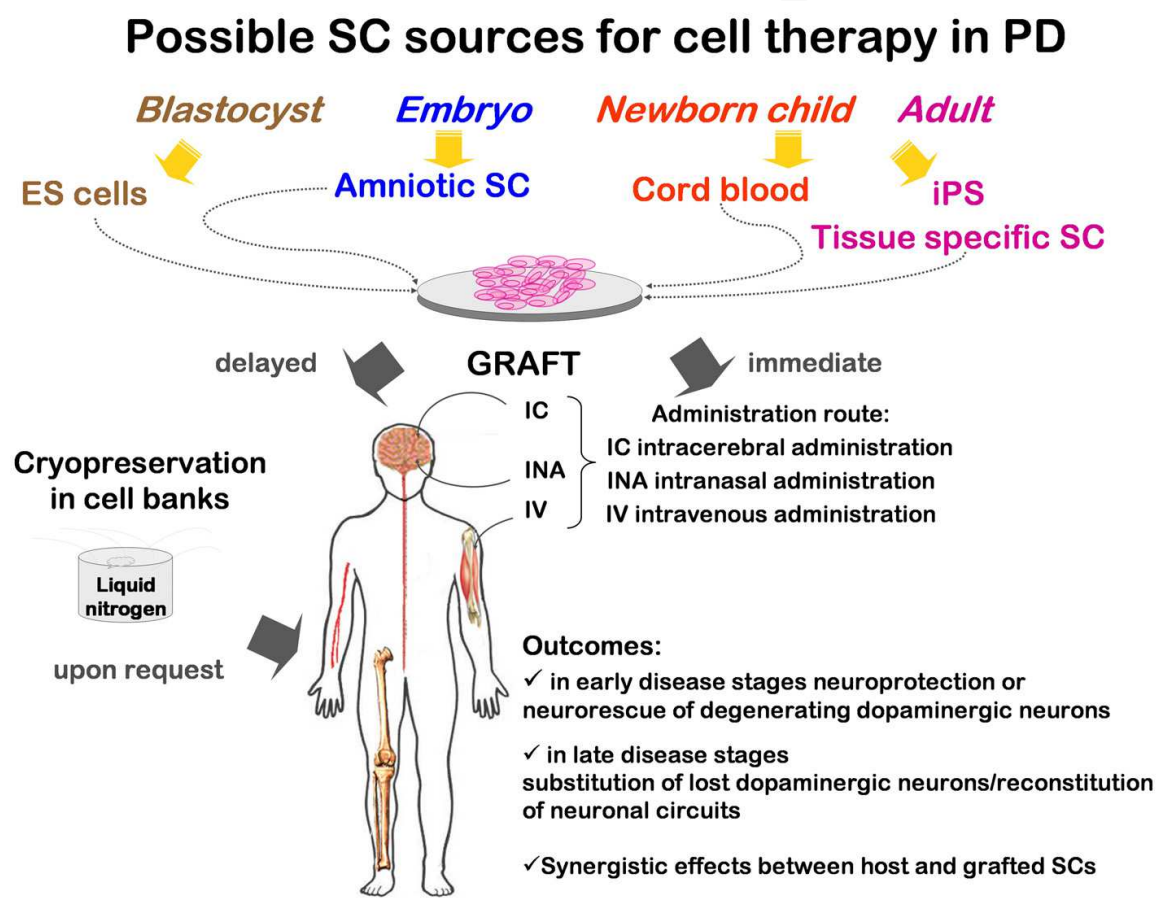


Fig. 2. Schematic flow chart for cell therapy in PD

A clinical approach to PD therapy will require 1) SC isolation (possible from different sources) 2) their expansion *in vitro* 3) direct or delayed transplantation through alternative or multiple administration routes. Independently from SC type and injection site, the therapeutic outcomes will depend upon donor and host ages, extension of the neuronal degeneration and graft size. The possible reparative mechanisms exerted by SC transplantation comprise neuronal replacement, neuroprotection of residual dopaminergic neurons and stimulation of endogenous neurogenesis, which may variably contribute to observed behavioral and physiological improvements. In PD cell therapy all the manipulations involving SCs should be conducted following the GMP guidelines in the absence of serum or other animal components.

Release of growth factor by grafted SC may influence adult neurogenesis and up-regulate self renewal and/or differentiation of adult host cells both under physiological and pathological conditions. Pre-clinical data suggest that modulation of endogenous neurogenesis may represent an alternative ways to slow down neuronal cell loss and possibly regenerate affected brain areas by modulation of endogenous neurogenesis (Geraerts et al., 2007; Okano et al., 2007). Administration of several growth factors (i.e. Transforming Growth Factor- α , BDNF and Fibroblast Growth Factor) in striatum enhanced neuronal differentiation within SVZ with overall improvements in murine behavior (Chiocco et al., 2007). Moreover, in the SNc pharmacological activation of dopamine receptor D3 with a selective agonist 7-hydroxy-N,N-di-n-propyl-2aminotetralin- induced cell proliferation and maturation towards dopaminergic phenotype (Van Kampen and Eckman, 2006), thus suggesting the possible occurrence of adult neurogenesis in this region under the pathological conditions in PD (Arias-Carrion et al., 2009). Presence of neurogenesis in the SNc suggests that disease progression may rely on the loss of dopaminergic neurons as well as on the malfunctioning in their turnover. Possible efficacy of orthotopic dopaminergic neurogenesis in PD has been questioned for a long time (Hermann and Storch, 2008), but transplantation experiments have indicated that several SC types, including neural precursors (Arias-Carrion et al., 2006; Madhavan et al., 2009) and MSC (Cova et al., 2010), can significantly support endogenous neurogenesis during the degenerative process in animal models of PD (Hess and Borlongan, 2008). Neurogenesis has been confirmed in SVZ of human brains (Curtis et al., 2007), but its physiological role is still uncertain (Zhao et al., 2008). Similarly, the existence of an improved neuronal reconstruction in the basal ganglia of the human PD brain (Yoshimi et al., 2005) is still a matter of debate. The reasons for decreased neurogenesis observed with aging and in pathological states may be related to an intrinsic inability to respond to the proliferative stimulation in the neurogenic niche, a reduction in the number of proliferative SC number, or the presence of activated microglia and neuroinflammation (Russo et al., 2011). Therefore, unraveling the localization as well as the degree of neurogenesis rate in human brains, together with the discovery of the specific molecules involved in these biological events, could lead to the discovery of new pharmacological disease-modifying treatments and novel potential targets, readily applicable to PD patients (Lindvall and Kokaia, 2010). Finally, it appears realistic to combine the synergistic effects between exogenous and endogenous SC actions to obtain cues on potential mechanisms involved in the noxious effects of neurodegeneration in PD as possible targets for clinical therapy (see Figure 2) (Madhavan and Collier, 2010).

7. Stem cell transplantation: Delivery method and timing

To date different SC types, as well as route of cell administration have shown efficacy in animal models. Two main routes have been generally used for SC delivery: intracerebral and intravascular. The first one is a stereotaxic transplantation of cells into the brain. Given, in PD, that brain damage principally occurs in both striatum (dopaminergic terminals) and SNc (neuronal soma), the best transplantation site, that would provide the most efficient and widest SC engraftment, is unknown. Nowadays, striatal administration of SCs is the most common approach for pre-clinical trials in PD (Blandini et al., 2010; Yasuhara et al., 2006; Zhu et al., 2009), although SC transplantation in mfb is also feasible (Gu et al., 2009). Gu and colleagues showed that double injection of NT-3 transfected NSC in mfb and ventral

tegmental area of parkinsonian rats generates new TH positive cells in these areas with relevant behavioral and functional recovery (Gu et al., 2009).

Although the intracerebral route has provided a large panel of positive results in animal models and has allowed a better understanding of mechanisms underlying disease pathology, independently of the graft site, an outsized dilemma still resides in its invasive nature. To bypass this concern intravascular administration has also been undertaken. Intravenous administration of MSC after in 6-OHDA lesioned rats yields preservation of dopaminergic system and relevant behavioral improvements, although no transplanted SCs were observed in brain one month after injection (Wang et al., 2010). The intravenous administration route has obvious clinical advantages compared to intracerebral injection, yet evident efficient therapeutic benefits are fully dependent on the appropriate number of cells reaching the lesion sites. Concordantly, Wang et al have reported that the majority of SCs injected intravenously mostly dispersed in pulmonary tissue (Wang et al., 2010). This is in high contrast with the intracerebral route in which a large amount of cells are injected directly in or may easily migrate within the nearer lesion site. In 6-OHDA lesioned rats, the number of SCs still present at the site of injection, 4 weeks after transplantation, was proportional to the number of cells initially injected (Cova et al., 2010). Regardless of the delivery route adopted for transplantation, the biological mechanisms activated by SC graft rely both on cellular replacement and activation of the endogenous repair mechanisms coupled to neurorescue effects exerted on degenerating neurons (Lindvall and Kokaia, 2010). To date, no data from comparative studies between several administration routes (e.g., intrastriatal, intraventricular, and intravenous injections) of SC delivery in PD patients are available, although open labeled clinical trials with stereotaxic surgery have been already conducted (Venkataramana et al., 2010). An interesting clinical approach by multiple administration routes for the treatment of spinal cord injuries has just been developed. Such strategy induces noteworthy with improvements of the life quality for patients (Geffner et al., 2008) and could be very positively applied to chronic degenerative diseases such as PD.

Recently, an innovative alternative route for SC administration via a intranasal drop has been developed in an animal model of PD. MSC delivered into rat nostrils were found to migrate to lesion brain areas where they survived for at least 6 months (Danielyan et al., 2011). In these animals striatal dopamine levels were increased and motor functions improved up to 68% of values observed in control animals (Danielyan et al., 2011). This administration route appears safe and could potentially be repeated overtime in a given patients. The intranasal procedure could avoid problems related to surgical implantation of SCs, although the positive outcomes need to be further confirmed before any clinical applications.

Future therapeutic trials should also evaluate how the time point at which SC transplantation is performed, with respect to the cerebral insult, may influence efficacy of the procedure: earlier cell grafts may provide effective neuroprotection to degenerating neurons but the hostile environment may endanger their long-term survival by spreading disease hallmarks (Kordower et al., 2008; Li et al., 2008; Mendez et al., 2008). In principle, a time interval sufficient to allow *in vitro* expansion of autologous SCs, would obviously be desirable both from a practical and clinical perspective. On the other hand, transplantation at later disease stages, when cell loss is almost complete, will mainly aim at replacing lost dopaminergic neurons and will certainly be affected by the reduced expression of homing signals secreted in degenerative brain tissues. Conversely, transplantation at early stage will mostly rely on rescue and regeneration of surviving neurons. For CNS repair,

transplantation of proliferating progenitors cells, whose fate is less predictable since they are more proliferative than neurons, would face difficulties in sorting from stray pluripotent SCs, in the absence of specific markers. A clear trial design will necessarily need to take in account all these different biological mechanisms and, most importantly, will require the development of the appropriate biomarkers (Rascol, 2009) to follow disease progression.

The choice of a specific SC type and its state of differentiation, as well as the amount of cells and route of administration will depend on the experimental endpoints, keeping in mind that each one faces inherent problems connected to local control of immune rejection, final differentiation towards dopaminergic neurons and cytokine release distally. For example transplantation of ES cells can lead to tumor formation and systemic injection of SCs may result in dispersion of the cells in non-target tissues. Circulating HSC could participate in the regeneration of peripheral tissues/organs, but only if a sufficient number of SCs is activated. Finally, as clearly pointed out by Irving Weissman, any future SC clinical application in neurodegenerative diseases will need to respect the four thresholds of clinical effectiveness: 1) cell homing to the diseased or injured tissue 2) effective engraftment, not just fusion with host cells 3) physiological effectiveness 4) permanence overtime (Weissman, 2000).

8. *In vivo* imaging and transplantation

As mentioned above animal models of PD are fundamental tools to evaluate feasibility and potential of a given SC population. To date translation of results obtained in pre-clinical animal models of PD has been difficult. In particular, the effect and long-term survival of transplanted cells remains an open issue. The development of innovative imaging techniques, combined with the creation of reporter transgenic mice, has widened our understanding of some pathological mechanisms of the disease and allowed the identification of specific pharmacological targets (van Nuenen et al., 2009). Precise tracking of transplanted SCs through novel imaging techniques, as well as monitoring of engraftment efficiency directly *in vivo* allows the immediate correlation between beneficial effects and SC localization/amount (Lee et al., 2008). Genetic tags have and continue to help researchers and bioethicists to track transplanted cells overtime following their behavior and dispersion in tissues in animals. The simplest tag uses genetic recombination to introduce a fluorescent marker, such as green fluorescent protein, into a cell, but magnetic nanoparticles have also been proven to be helpful (Ferreira et al., 2008). Since cell therapy relies on SC involvement in physiological circuits their upshots could persist over a long time and should, therefore, be devoid of side effects. Homing, engraftment, cell fate, persistence and tumor formation of labeled SCs and their progeny needs to be carefully evaluated and could potentially be assessed using *in vivo* imaging. In complex neurodegenerative diseases, such as PD, grafted SCs or derived progenitor cells may protect residual neurons rather than replacing the degenerated ones. Therefore, tagged grafts could be easily characterized to determine if transplanted cells trigger endogenous mechanisms of repair or whether they directly replace lost cell populations. Successful application of magnetically-labeled mouse embryonic SCs to a rat model of PD coupled to the study of their diffusion up to 6 months post transplant has already demonstrated the feasibility and safety of this approach (Stroh et al., 2009). Imaging techniques are already used to study early and presymptomatic stages of PD (Wu et al., 2011) and effectively measures outcomes in clinical trials of neuroprotection demonstrate

that it is a practical non invasive method extensible to all PD patients (Pavese et al., 2009). PET measurements of 6-(18F) fluorodopa (18F-FDOPA) uptake indicate nigrostriatal neuronal integrity and may provide a useful endophenotype for PD linkage studies (Kumakura and Cumming, 2009). Clinical benefits and graft viability of embryonic dopamine cell implantation have been followed by functional imaging for up to 4 years after graft in 33 patients, thus correlating motor improvements with increased 18F-FDOPA uptake (Ma et al., 2010).

9. Conclusions

Gaining more information about the pathology of the disease, the probable behavior of the grafted cells, as well as the reciprocal interconnections between the transplants and the host environment in animal models will be useful to predict possible complications and undesirable side effects readily translatable to future clinical trials for PD patients (Li et al., 2010b). Caution needs to be adapted since xenograft models of disease in animals may not accurately predict the same response in humans due to inherent differences. However, pre-clinical data will help improve patient selection for future clinical trials, assess restoration of brain connectivity, and monitor inflammatory processes in the continuous search of novel therapeutic targets (Politis and Piccini, 2010). Moreover, targeted delivery of SCs through alternative routes could be easily compared in animal models. Concordantly, one objective of modern neuroimaging is to identify markers for clinical diagnosis, monitor the disease progression, define the exact SC placement and analyze the impact of long-term drug/cell therapy through the direct spatio-temporal visualization of SCs as well as their effect on disease progression in patients, using non invasive techniques (Lee et al., 2008). A successful SC therapy requires extensive knowledge on SC properties, appropriate harvesting, manipulation and apt implantation, but also subsequent graft monitoring in the long time to verify the permanence of reparative mechanisms (Nikolic et al., 2009). On the basis of these data, it may be possible to properly select SC type, administration timing and delivery route for specific disease entities, anatomic areas, and physiologic circumstances to obtain reproducible experimental results for the creation of effective clinical protocols (Lindvall and Kokaia, 2010).

Additionally, cell transplantation in animal is often performed before or contemporaneously to neurotoxin lesion. Further development of experimental models that more accurately recreate neurodegenerative conditions present in patients, in which treatment can only intervene when the degenerative process is overt and motor symptoms are manifest, is required. In particular, the creation of genetic animal models is becoming increasingly important to elucidate gene-environment interactions, define pathogenic mechanisms, and provide a platform for testing cell therapeutic interventions (Magen and Chesselet, 2010).

The development and validation of conventional pharmacological therapy for clinical use is a long process that usually requires at least a decade. Cell transplantation, which represents an advanced therapeutic strategy far more complex than any pharmaceutical compound, was introduced surprisingly early into the clinic. Although some positive effects have been observed in the pioneering clinical studies sufficient caution should be taken before this strategy can be "routinely" applied to PD patients in order to avoid complications that may set back the field. In particular, defining and validating a specific cell type that may be consistently used in transplantation procedures is still a milestone that needs to be achieved. Extensive interactions and communication between clinicians and pre-clinical scientists is

mandatory to allow the constant fine-tuning of the design of therapeutic strategies for PD patients.

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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of α -synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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