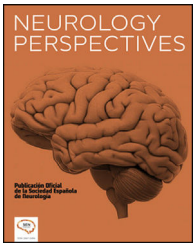
Neurology Perspectives 2 (2022) S58–S68

NEUROLOGY PERSPECTIVES

www.journals.elsevier.com/neurology-perspectives



REVIEW

Parkinson's disease: Present and future of cell therapy

F.J. Sancho-Bielsa*

Área de Fisiología, Departamento de Ciencias Médicas, Facultad de Medicina de Ciudad Real, Ciudad Real, Spain

Received 27 July 2021; accepted 29 July 2021

KEYWORDS
Neurodegenerative disease;
Parkinson's disease;
Cell therapy

Abstract Parkinson's disease (PD) is the second most frequent degenerative disease and is characterised by dyskinesia, postural instability, and tremor due to selective loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc). Early approaches to the management of PD aimed to alleviate symptoms using pharmacological treatments. However, not all patients tolerate drugs equally and due to the progressive course of the disease, medication needs to be adjusted over time. Furthermore, most patients are elderly individuals with concomitant diseases, which increases the risk of drug–drug interactions. In this context, the discovery of adult neurogenesis has caused a dramatic change in the therapeutic approach, aiming to repair the nervous system. However, cell replacement therapies alone have been unable to solve this situation, as they do not modify the underlying neurodegeneration. For this reason, the solution may lie in combining different approaches. There is a need to identify early biomarkers that may be detectable before onset of neurodegeneration, to identify and apply more appropriate pharmacological treatments for the early stages of the disease, to tailor pharmacological treatments, and to use cell replacement therapies, taking into account the need to reprogram the cells used and to avoid as many adverse effects as possible, including immune reactions and tumours. The future of PD treatment represents a significant challenge due to its heterogeneity.

PALABRAS CLAVE
Enfermedad neurodegenerativa;
Parkinson;
Terapia cellular

Enfermedad de Parkinson: presente y futuro en los tratamientos con terapia celular

Resumen La enfermedad de Parkinson (EP) constituye la segunda enfermedad degenerativa más frecuente, caracterizada por la discinesia, inestabilidad postural y temblores debido a una pérdida selectiva de neuronas dopaminérgicas de la pars compacta de la substantia nigra (SNpc). El enfoque inicial para de la EP ha consistido en aliviar la sintomatología del paciente mediante el uso de tratamientos farmacológicos. Sin embargo, no todos los pacientes toleran los medicamentos de igual modo y al tratarse de un trastorno progresivo, se hacen necesarios ajustes en la medicación a lo largo de tiempo. Además, la mayoría son pacientes geriátricos con

* Corresponding author at: Facultad de Medicina de Ciudad Real, UCLM, Camino de Moledores s/n, 13071 Ciudad Real, Spain.
E-mail address: Francisco.sancho@uclm.es.

https://doi.org/10.1016/j.neurop.2021.07.006

enfermedades concomitantes, lo que puede ocasionar interacciones con otros fármacos. Pero con el descubrimiento de la neurogénesis adulta se genera un cambio drástico en el enfoque terapéutico para la reparación del sistema nervioso. Sin embargo, las terapias de reemplazo celular se han mostrado incapaces de solucionar el problema por sí solas, dado que no modifican la neurodegeneración subyacente. Por este motivo, la solución podría pasar por una combinación de enfoques. Es necesario encontrar biomarcadores tempranos, previos a que se manifieste la neurodegeneración, identificar y aplicar los tratamientos farmacológicos más adecuados para las fases iniciales de la enfermedad, realizar el tratamiento farmacológico de manera personalizada y emplear terapias de reemplazo celular, teniendo en cuenta la necesidad de reprogramar las células empleadas y evitar todos los efectos adversos posibles como reacciones inmunitarias o generación de tumores. El futuro en el tratamiento de la EP constituye todo un desafío dada su heterogeneidad.

Introduction

As a result of the increase in life expectancy and therefore in the mean age of the population, neurodegenerative diseases have become a major problem worldwide. Significant research efforts are currently being made to study the aetiopathogenesis of these diseases, but as their origins are still unknown, treatment is exclusively symptomatic.

Our understanding of the brain has changed. In the second half of the 20th century, researchers observed the division of glial cells in the mouse brain[1]; the migration of postnatal neuroblasts from the subventricular zone to the olfactory bulb, showing the neurogenesis process in the adult brain[2]; and subsequently the presence of neurons born in the dentate gyrus of adult rats[3] and the vocal control nucleus of birds,[4] as well as the proliferation of progenitor cells. However, endogenous neurogenesis has been observed not only in vertebrates and lower mammals, but also in humans and other primates; this biological process has recently also been described in human adults.[5]

Although the adult central nervous system presents only a limited capacity for self-repair, as a result of these findings, the brain is no longer understood as a static structure, drastically changing therapeutic approaches in regenerative medicine for the central nervous system. Stimulation of these physiological processes, transforming neural stem cells into specialised neuronal cells, would represent one means of treating neurodegenerative diseases.[6] However, the great complexity of neurodegenerative diseases has led to the development of multiple therapeutic alternatives with very varied results.

Parkinson's disease: Pathogenesis and role of protein aggregation

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and the second most frequent neurodegenerative disease. In Europe, the prevalence and incidence rates of PD are estimated at 108–257 cases per 100,000 population and 11–19 cases per 100,000 person-years, respectively. Risk factors include older age, male sex, and certain environmental factors.[7] PD is a progressive neurodegenerative disease characterised by dyskinesia, postural instability, and tremor, caused by selective loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc); it is also characterised by involvement of the nucleus basalis of Meynert[8] and the presence of intraneuronal protein deposition, with Lewy bodies and neurites, composed of α-synuclein and a ubiquitin monomer.[9] The death of dopaminergic cells of the SNpc disrupts the motor control network of the basal ganglia, causing typical motor symptoms (bradykinesia, tremor, rigidity, and speech and gait alterations).

In healthy tissue, production of α-synuclein is strictly regulated, whereas in PD, accumulation of α-synuclein protein monomers and aggregates is observed.[10]

Mitochondrial dysfunction, oxidative stress, and microglial impairment are other factors associated with PD and other neurodegenerative diseases.[11]

Post-mortem studies of the brains of patients with PD have shown a deficiency in the electron transport chain in the substantia nigra.[12] The inhibition of mitochondrial respiratory complexes generates neuronal apoptosis mediated by oxidative stress. Mutations in such genes as *parkin* and *PINK1* have been detected in patients with PD.[13] As these genes play a vital role in mitophagy, mutations trigger mitochondrial dysfunction and causes autosomal recessive PD.[14]

Experimental models used in Parkinson's disease

With a view to better understanding PD, models have been developed that seek to reflect the disease as reliably as possible; these include yeast, mouse, fruit fly, and non-human primate models. The first approach consisted of direct injection to the central nervous system of 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to replicate dopaminergic cellular death in the SNpc. This method enabled researchers to determine the effects of blocking dopamine (DA) expression, but did not replicate the underlying neurological pathology. Furthermore, mouse models have shown that overexpression of human risk factors, such as the α-synuclein gene (*SNCA*), is associated with an age-dependent degeneration of

dopaminergic neurons, similar to that observed in the human pathological phenotype.[15,16] These findings support the causal role of α-synuclein in disease progression, but currently lack any clinical application.

Treatments for Parkinson's disease

Until the recent development of promising strategies involving the use of human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) in models of an existing PD state,[17,18] advances have been made using treatments with different approaches: pharmacological, surgical, and modification of the course of the disease.

Pharmacological therapies

The pharmacological approach aims to alleviate PD symptoms, as no traditional drug has shown a neuroprotective effect against the disease[19]; in other words, they do not act on the underlying neurodegeneration.[20]

The most effective pharmacological treatment is levodopa, a DA precursor, combined with a peripheral decarboxylase inhibitor.[20] Levodopa is the gold-standard treatment, and is highly effective during the first stages of the disease. However, significant issues arise in the long-term, also reducing its therapeutic effectiveness.[21] Combination therapy with carbidopa (Lodosyn) and levodopa is usually administered; this prevents or mitigates such adverse effects as nausea. Inhaled levodopa (Inbrija) may be administered to control the symptoms that appear when the effects of oral drugs wear off; likewise, levodopa may be administered directly to the small intestine using a feeding tube (Duodopa).

As the disease progresses, the benefits of levodopa may become less stable and the patient may start to present involuntary movements after taking higher doses of levodopa.

It should be noted that PD usually presents in geriatric patients with concomitant diseases, who are frequently using other drugs, which increases the risk of adverse effects due to possible drug–drug interactions and contraindications.[22] Clearly, pharmacological treatment of PD is complex and requires expertise.[23] Furthermore, adjustments must be made over time due to the progressive nature of the disease. When symptoms are mild, patients may function adequately without symptomatic treatment; however, the use of well-tolerated agents in early stages and in the absence of functional impairment provides better long-term results.[19]

The most frequently used drugs are monoamine oxidase-B (MAO-B) inhibitors that interfere with DA degradation, such as selegiline (Zelapar), rasagiline (Azilect), and safinamide (Xadago), which are useful early therapies[24]; such neuroprotective drugs as MAO-B inhibitors with propargylamine derivatives, which inhibit oxidative deamination of DA, preventing the generation of oxygen free radicals that can damage nigrostriatal neurons and present antiapoptotic properties; and coenzyme Q10, an antioxidant component whose levels are reduced in patients with PD and with proven neuroprotection against neurodegenerative diseases.[25] Such catechol-O-methyltransferase inhibitors as entacapone (Comtan), opicapone (Ongentys), and tolcapone (Tasmar) have also been used; these drugs enhance the effects of levodopa, improving its bioavailability, but have no symptomatic effects in the absence of levodopa. Similarly, DA agonists, classified as ergoline derivatives (bromocriptine, pergolide) and non-ergoline derivatives (pramipexole, ropinirole, and rotigotine), have also been used. These drugs are efficacious in monotherapy in mild to moderate cases of PD, and to supplement levodopa.[26,27] DA agonists including rotigotine (Neupro) may be administered in patches, or fast-acting apomorphine injections (Apokyn) may be used.

Anticholinergic drugs reduce the effects of the degeneration of nigrostriatal dopaminergic neurons. DA deficiency, which tonically inhibits striatal cholinergic neurons, leads to increased cholinergic activity.[28] Several anticholinergic drugs are currently available, including benztropine (Cogentin) and trihexyphenidyl.

Amantadine presents moderate symptomatic effects. Although the precise action mechanism remains unknown, both dopaminergic and non-dopaminergic mechanisms are involved. It is also useful for suppressing levodopa-induced dyskinesia.[27] Dyskinesia is treated by reducing doses of dopaminergic drugs or adding amantadine.[24]

In young patients with prominent tremor, such anticholinergic agents as trihexyphenidyl are useful, although precautions should be taken due to their potential adverse effects, particularly those related to cognition.[24] Contrary to the initial therapeutic approach, in which levodopa was avoided in early treatment, recent research does not support this approach.[29]

DA agonists are associated with a higher overall risk of adverse events.[30] The majority of patients with PD simultaneously use several classes of drugs to complement their benefits, limiting high doses and doses related to adverse events.

Surgical treatments

Surgical treatment, which has contributed to improving our understanding of the pathophysiology of PD, is indicated when pharmacological treatment is insufficient to control symptoms throughout the day. However, its effectiveness is limited to such motor symptoms as bradykinesia, rigidity, tremor, and drug-induced dyskinesia.[31]

The initial surgical approach to PD was limited to lesion procedures, such as the first pallidotomies[32,33] performed to treat motor symptoms. However, deep brain stimulation has since become the predominant therapy, representing one of the most influential advances since levodopa, lowering doses of the drug and improving tremor.[34] The procedure is reserved for cases of advanced PD with motor complications and/or drug intolerance that lead to poor quality of life.

Surgical approaches have improved with current imaging techniques (high-field magnetic resonance imaging, tractography, and functional images), optimising surgical precision and reducing adverse effects. However, the current aim is to develop less invasive therapies that do not require open surgery.

Disease-modifying treatments

The above-mentioned therapies treat the motor symptoms of PD but do not alter its course; therefore, researchers have aimed to find alternative treatments that may modify the underlying neurodegeneration, such as gene therapy, immunotherapy, or cell replacement therapies.

Gene therapy

Clinical trials of gene therapy have aimed to alter enzymes and neurotrophic factors in the basal ganglia. It is able to safely induce expression of specific proteins; however, its clinical effectiveness has not met expectations.[35] Some animal studies show that gene therapy is viable and safe,[36–38] although concerns have been raised due to the introduction of viral material to the brain that may possibly reach surrounding areas. Techniques are being researched to overcome these issues, as well as the use of alternative vectors.[39] Infusion of the gene encoding glutamic acid decarboxylase, the enzyme responsible for GABA synthesis, via a virus into the subthalamic nucleus of patients with advanced PD[40] caused no adverse events but was associated with improvements, substantially reducing thalamic metabolism restricted to the treated hemisphere. However, this study did not include a control group and the placebo effect can be considerable in PD; therefore, definitive conclusions on the efficacy of the treatment cannot be drawn.

Animal models have shown that the glial cell-derived neurotrophic factor (GDNF) presents neuroprotective, neurorestorative, and neurological rescue effects.[41] Whereas intracerebroventricular injection of GDNF[42] is ineffective and is associated with significant adverse effects, administration to the putamen using an infusion pump improved the quality of life of some patients.[43] However, another trial including a placebo group identified no significant improvements.[44]

Immunotherapy

Immunotherapy has been postulated as a potential disease-modifying treatment, using specific antibodies targeting misfolded α-synuclein; however, although trials have shown the safety and tolerability of the treatment, its clinical effectiveness seems to be limited.[45]

Cell replacement therapy

The discovery of adult neurogenesis led to a drastic change in therapeutic approaches to repairing the nervous system; therefore, the next step after neuroprotection is cell replacement therapy.

Clinical trials have been performed in patients with advanced PD showing resistance to pharmacological treatment. Although the optimal candidates for cell transplantation are yet to be identified, young patients with moderate PD may be the most appropriate.[46,47]

Grafts of foetal mesencephalic tissue are able to decarboxylate and release DA and mediate a delayed restoration of activity in prefrontal areas of motor circuits.[48,49] Graft survival and growth has been demonstrated in morphological studies, whereas the presence of synaptic contacts with host striatal neurons has been confirmed in ultrastructural studies.[50] Graft neurons may reinnervate the striatum and restore neural transmission through the basal ganglia. However, methodological differences, both in cellular preparation and transplantation, may lead to diverging results. Transplantation of dissociated tissue (cell suspension) seems to be more effective than solid grafts,[51] which would cause more inflammation and gliosis. It is also important to consider the distribution, anatomical location, and heterogeneous cellular composition of grafts.

The foetal dopaminergic neurons transplanted into the striatum probably act in two ways[52]: (i) as pharmacological agents, they release DA and increase concentration of the neurotransmitter in the striatum; and (ii) in a physiological sense, they reinnervate the striatum by axonal outgrowing and synaptic reconnection, with subsequent regulated DA release, which would prevent the onset of adverse effects, including dyskinesias. However, with current cell preparation and transplantation methods, transplanted dopaminergic neurons are likely to act in both ways. Therefore, the main objective of cell therapy may not be limited to correcting DA deficiency; rather, it may also aim to restore or re-establish connectivity and physiology[53,54]; this is challenging as transplanted cells, in addition to their ectopic location in the brain, present low survival rates. Despite this, the total number of cells exceeds that required for presence of parkinsonism at PD onset.[50,55]

Several clinical trials at different stages of development are using autologous and non-autologous cells, including hESCs and iPSCs.[56] Over the past two decades, DA-releasing cells from the human foetal ventral mesencephalon have been transplanted to patients with advanced PD, obtaining poor results.[46,47,57–60]

Grafts of foetal ventral mesencephalic cells survive and reinnervate the brain, restoring motor function and causing prolonged symptom improvement. However, poor survival of the graft has been reported in some patients; together with the need for foetal donors, this has led to limited use of this therapy.

Despite the sustained, moderate improvement in Parkinsonian symptoms and the mild reduction in levodopa-induced dyskinesias,[57,53] most patients required concomitant treatment with levodopa in order to obtain significant motor improvements; however, due to the presence of dyskinesia secondary to treatment, transplantation is not recommended as a routine therapeutic option.

The inefficacy of foetal grafts in reverting parkinsonism in advanced stages of PD may be explained by progression of the disease, as it spreads beyond the substantia nigra.

The normalisation of neuronal activity in premotor cortical areas suggests a sequential development of events: cell survival, integration, functioning of cells transplanted into the striatum, and long-term motor benefit.[48,49] However, this depends on multiple variables such as the surgical technique used, the level of immunosuppression, cellular preparation and survival, and patient selection.

Double-blind, placebo-controlled studies[46,47] have shown minimal, transient improvement of parkinsonism in patients with PD undergoing transplantation of foetal dopaminergic cells, in comparison with the sham surgery group; this contrasts with the findings of open trials, in which patients showed sustained improvement for over 10 years. These differences may be explained by the immunosuppressive

treatment used. Deficient immunosuppression would impair cell survival due to the presence of inflammatory processes, affecting the viability of transplanted cells and subsequently clinical recovery.

The preparation and composition of the graft are determining factors of effectiveness and survival. Tissue dissection, differences in foetal age, storage after dissection, and the method of dissociation before graft (in pieces or raw cell suspension) may explain the different results obtained. Cell survival may be compromised due to long cold storage times. Transplantation of dopaminergic cells from inappropriate areas, as well as the proportion of serotonergic neurons in the graft, may explain the onset of dyskinesias in animal models.[61,62]

The integrity of ascending extranigral dopaminergic pathways is essential for achieving a significant and sustained motor benefit. Patients with dopaminergic denervation exclusively affecting the nigrostriatal pathway present sustained improvement of parkinsonism, but if denervation is more extensive, no motor improvement is experienced after transplantation. As a result, grafts may only be useful in the early stages of PD, when the integrity of the ascending dopaminergic pathways is still preserved,[63] although this correlation has not been observed in all clinical trials.[64]

Transplantation of the graft is essential in obtaining the greatest benefits. Restoring dopaminergic levels within the subthalamic nucleus by grafting dopaminergic cells is essential to achieving complete motor recovery, according to some studies.[65]

However, the use of foetal tissue presents some ethical and practical issues, such as immunological rejection and the difficulties of obtaining tissue, which has led to a search for new sources of dopaminergic neurons for transplantation. Some studies have transplanted carotid body cells, which constitutes a reliable and safe procedure.[66,67] Clinical findings showed a mild, non-significant improvement in parkinsonism, but no dyskinesias.

Retinal cells transplanted to the striatum would act as a DA pump, and have been shown to promote cell survival in cultures of dopaminergic cells due to the trophic factors they release. In animal models, retinal cells led to a significant and sustained motor recovery. One study of patients with PD confirmed these data, showing a moderate clinical benefit but no dyskinesias.[68,69]

Stem cells are another source for cells for transplant. It is possible to induce differentiation into functional neurons with correct cell and regional identity. However, these populations are heterogeneous and require careful purification to prevent uncontrolled proliferation or differentiation into undesired phenotypes. As a result, protocols have been developed in recent years to induce dopaminergic differentiation, but are yet to be well established.

One advantage of stem cell therapies is that they provide trophic signals to help certain cell populations and/or replace lost cells. In addition to the scarce neurogenesis in adult patients, cell survival also represents a serious problem.

Several sources of stem cells have been suggested for PD treatment, with each case presenting pros and cons. The most frequent sources are embryonic stem cells (ESC), mesenchymal stem cells (MSC), iPSCs, and neural stem cells (NSC).[70,71,72,73]

Mesenchymal stem cells

MSCs are a series of pluripotent stem cells generally isolated from the bone marrow,[74] placenta,[75] amniotic fluid,[76] umbilical cord blood,[77] or adipose tissue.[78] They present low tumorigenicity and immune response, compared to ESCs and iPSCs, due to the lack of major histocompatibility complex type II molecules.[79]

Schiess et al.[80] underscore the relevance of neuroinflammation in PD pathogenesis and suggest the use of allogeneic bone marrow-derived MSCs as an immunomodulatory therapy.

Neural stem cells

NSCs are multipotent, self-renewing stem cells that may differentiate to such neural cells as dopaminergic cells, oligodendrocytes, and astrocytes.[81] NSCs can be collected from foetal, neonatal, or adult brain regions, including the subventricular zone (SVZ), the subgranular zone (SGZ), and the subependymal zone (SEZ) of the lateral ventricles.[82–85] Bilateral intraputaminal grafting of dopaminergic neurons derived from the ventral tegmental area leads to clinical benefits in younger patients, but not in elderly patients with PD.[46,47]

Embryonic stem cells

ESCs are pluripotent stem cells derived from the internal cellular mass, and present high proliferative potential to differentiate into cells of the three germinal layers, including dopaminergic neurons.[86] They are excellent candidates for generating DA-producing cells with a high proliferative potential, although they do present some issues.

Induced pluripotent stem cells

iPSCs are adult cells that are genetically reprogrammed to create cells similar to ESCs through the expression of genes and cellular factors (OCT4, SOX2, Klf4, c-Myc, NANOG, and LIN28). There are considerable similarities between iPSCs and ESCs, but iPSCs present a practical solution to the problem of the immunogenic response.[87] Dopaminergic neurons derived from self iPSC transplants are able to survive in the brain without immunosuppression, and/or improve motor and non-motor symptoms of PD.[88–93]

Directly induced dopaminergic neurons

Transdifferentiation is defined as the direct transformation of a somatic cell into another cell type without a pluripotent stage.[94,95] Fibroblasts can be reprogrammed for direct transformation into functional dopaminergic neurons.[96] This technique is faster than obtaining dopaminergic neurons from iPSCs.

In short, several recent clinical trials have shown some advantages and disadvantages; several other trials are currently at different stages of development (Table 1).

Table 1 Clinical trials using stem cells in patients with Parkinson's disease, extracted from ClinicalTrials.gov.

Full title of the clinical trial	Stage	Location
• Allogeneic bone marrow-derived mesenchymal stem cell therapy for idiopathic Parkinson's disease	Completed	Houston, Texas, USA
• Umbilical cord derived mesenchymal stem cells therapy in Parkinson's disease	Enrolling by invitation	Shijiazhuang, Hebei, China
• Use of mesenchymal stem cells (MSCs) differentiated into neural stem cells (NSCs) in people with Parkinson's (PD).	Recruiting	Amman, Jordan
• Autologous mesenchymal stem cell transplant for Parkinson's disease	Completed	Mumbai, Maharashtra, India
• Phase 1 safety and tolerability study of MSK-DA01 cell therapy for advanced Parkinson's disease	Recruiting	Orange, California, USA New York, New York, USA Toronto, Ontario, Canada
• Parkinson's disease therapy using cell technology	Recruiting	Minsk, Belarus
• Phase IIa randomised placebo controlled trial: mesenchymal stem cells as a disease-modifying therapy for iPD	Recruiting	Houston, Texas, USA
• A study to evaluate the safety and efficacy of human neural stem cells for Parkinson's disease patient	Unknown	Suzhou, Jiangsu, China
• Randomised, double-blind clinical trial for Parkinson's disease (early and moderate)	Recruiting	Sugar Land, Texas, USA
• Safety and efficacy study of human ESC-derived neural precursor cells in the treatment of Parkinson's disease	Unknown	Zhengzhou, Henan, China
• Individual patient expanded access IND of HB-adMSCs for the treatment of Parkinson's disease	Not available	Sugar Land, Texas, USA
• A study to evaluate the safety of neural stem cells in patients with Parkinson's disease	Unknown	Melbourne, Victoria, Australia
• Study to assess the safety and effects of autologous adipose-derived SVF cells in patients with Parkinson's disease	Withdrawn	Aventura, Florida, USA
• Neurologic stem cell treatment study	Recruiting	Westport, Connecticut, USA Coral Springs, Florida, USA Dubai, United Arab Emirates
• Individual patient expanded access IND of Hope Biosciences autologous adipose-derived mesenchymal stem cells for Parkinson's disease	No longer available	Sugar Land, Texas, USA
• Potential use of autologous and allogeneic mesenchymal stem cells in patients with multiple system atrophy	Recruiting	Jakarta Pusat, DKI Jakarta, Indonesia
• Using [18F]FDOPA PET/CT to monitor the effectiveness of foetal dopaminergic grafts in Parkinson disease patients	Unknown	Saskatoon, Saskatchewan, Canada
• Mesenchymal stem cells transplantation to patients with Parkinson's disease	Unknown	Guangzhou, Guangdong, China
• Rajavtihi neuronal adult stem cells project	Draft	Bangkok, Thailand
• Parkinsonian brain repair using human stem cells	Unknown	Mexico City, Mexico
• Development of iPS from donated somatic cells of patients with neurological diseases	Recruiting	Jerusalem, Israel

Pluripotent and multipotent stem cells present fundamental differences in proliferation and differentiation capacity. Neural stem cells are multipotent and tissue-specific, and may be isolated from the foetal or the adult central nervous system.[97] These cells differ from pluripotent stem cells in their limited proliferation capacity and in the regionally restricted number of mature phenotypes that they may generate.[98] Neural stem cells proliferate in response to mitogens and can be cultured and propagated in-vitro in aggregates or neurospheres. Progenitor cells in neurospheres maintain the ability to generate neural and glial lineage cells after the removal of mitogens, although after a prolonged in-vitro passage, their differentiation capacity is fairly limited.[99]

Unlike stem cells from adults, ESCs do not seem to present limitations for differentiation into any type of somatic cell, including mesencephalic dopaminergic cells. Induction protocols and culture systems have been optimised to generate mouse[100] and primate dopaminergic cells,[101] and hESC lines.[102] Other pluripotent stem cells, such as

parthenogenetic stem cells,[103] stem cells from somatic cell nuclear transfer (SCNT),[104] and iPSCs,[105,106] may also differentiate into specific somatic phenotypes for application in replacement therapies.

The most recent advances in cell reprogramming and personalised medicine enable physicians to perform cell therapies and specific treatments that were previously out of reach, by using iPSCs that selectively differentiate into dopaminergic neurons. Unlike other models, when using iPSCs, endogenous cellular machinery and transcriptional feedback are preserved; this is essential in such a genetically complex pathology as PD. These techniques are able to generate iPSC lines with specific genetic risk factors, enabling researchers to assess the response to treatment in different genetic subpopulations. iPSC lines may be genetically corrected and transplanted to a patient with a view to restoring function.[107] The advantage of iPSCs lies in the fact that they are specific to the patient, reducing the risk of immunological rejection.

Cell transplant strategies for replacing dopaminergic cells are a promising approach, thanks to the use of biocompatible materials. Biomaterials offer a novel approach to stimulating endogenous neurogenesis and may help in the transplantation of neural progenitor cells, providing a tissue-appropriate physical and trophic milieu for the newly integrating cells.[108] The use of biomaterials would improve the survival of grafts by providing an appropriate microenvironment for cells, favouring their adhesion and growth. Biomaterials may be used as support for cellular growth and subsequently be transplanted. Numerous biomaterials have been developed, with different characteristics (hydrogels, nanoparticles, self-assembling peptides, nanofibres, and carbon-based nanomaterials).[109] Although more studies are needed before they can be used in humans, the results obtained have been very promising, and they therefore represent a potential therapeutic approach for neurodegenerative diseases.

Table 2 Advantages and disadvantages of cell therapy (adapted from Ghamgosha et al.[130]).

Stem cells	Advantages	Disadvantages
NSC	1. Lower tumorigenicity and immune response than ESCs and iPSCs 2. Capacity to form neurons, astrocytes, and oligodendrocytes	1. Risk of graft-induced dyskinesias 2. Limited in-vivo differentiation 3. Similar symptoms to PD 4. Do not differentiate into cells from the three germinal layers
MSC	1. Lower tumorigenicity and immune response than ESCs and iPSCs 2. Genuine and accessible cell source 3. Improve cognitive and motor performance	1. Limited therapeutic effectiveness in humans 2. Do not differentiate into cells from the three germinal layers
ESC	1. High proliferative and differentiation potential 2. May generate dopaminergic neurons 3. May differentiate into cells from the three germinal layers	1. Risk of tumour development 2. Genomic instability 3. Immunogenic response and ethical issues
iPSC	1. High proliferative and differentiation potential 2. May generate dopaminergic neurons 3. May differentiate into cells from the three germinal layers 4. No immunogenic response or ethical issues	1. Risk of tumour development 2. Genomic instability

Limitations of cell therapy

One of the most frequent disadvantages of using ESCs and iPSCs is the risk of tumour formation and genomic instability (Table 2). However, MSCs present mild immunogenic responses, due to the lack of major histocompatibility complex type II.[79]

MSCs present relatively poor therapeutic effectiveness in humans. NSCs present low proliferation capacity and differentiation rates, and lose their characteristics after repeated passages.[110] The use of ESCs poses several problems. Their genomic instability, immunogenic responses, the possible rejection of the graft, tumorigenicity, and ethical issues represent significant limitations; therefore, clinical trials with ESCs are yet to be performed in patients with PD. While iPSCs present practically no ethical problems, the immunogenic response, graft rejections, and ectopic overexpression of Klf4, Oct4, Sox2, and c-Myc may lead to the formation of breast tumours,[111] epithelial cell dysplasia,[112] mucinous colorectal cancer,[113] and human cancer,[114] respectively.

Furthermore, the combination of several viral structures within the host genome may lead to the development of teratoma.[115] Induced dopaminergic neurons are unable to express some specific markers of mesencephalic dopaminergic neurons, and the effectiveness of conversion is low (10%).[116] Furthermore, fibroblasts in patients with PD may carry genomic mutations.

Conclusions

All the advances made to date have contributed to our understanding of PD; however, the disease involves dysfunction of multiple systems and neurotransmitters that cause similar symptoms. From a pharmacological perspective, the variability of responses to levodopa may indicate the presence of multiple biochemical mechanisms of neurodegeneration; which would result in a need for diverse treatments with different approaches.[117,118]

Treatment is currently personalised according to the patient's expectations, level of disability, employment status, and functional and chronological age, the expected effectiveness and tolerability of drugs, and the response to previous PD therapies[19]; however, many other factors must also be considered. As no early markers of PD have been identified, many dopaminergic neurons of the substantia nigra will already have died by the time motor symptoms

manifest. Therefore, it seems logical to consider cell replacement approaches to achieve restoration.

Since the discovery that foetal transplants may revert Parkinsonian signs in mice models,[119,120,121] neural transplantation has aimed to replace the neurons lost due to neurodegenerative processes; however, the clinical effectiveness and application of these techniques are limited by the scarcity of donors of human foetal neural tissue.

Both hESCs and iPSCs present unique characteristics that make them the ideal candidates for research into the development of PD.[122] Stem cells may adapt to differentiate into a series of cell fates, including SNpc dopaminergic cells that modulate PD at the cellular level.[123,124] Induced stem cells present the advantage of being specific to the patient, which could shed light on the individual contribution of each risk factor for the different mutations associated with PD in a phenotypically similar state.

Researchers have applied and widely reviewed the new genetic reprogramming techniques (TALEN, CRIPSR)[125,126]. The development of gene editing tools enables research into neurodegenerative mutations, and genetic screening will enable us to better understand disease progression and specific treatments. The influence of specific genetic factors may explain part of the variability in patients' responses to pharmacological treatment. These genetic differences would play an important role in drug metabolism pathways, which would explain the different responses to treatment.[127,128]

Genetic factors, together with sex, have an impact on treatment, as it has been observed that polymorphisms of the dopamine D2 receptor gene have protective effects in men but not in women.[129] Genetic differences may also be influenced by epigenetic factors.

The new techniques being developed include optogenetics, magnetogenetics, and sonogenetics, which offer interesting possibilities, such as treatments aiming to provoke genetic alterations and modulation of the brain circuitry.

The growing body of knowledge on PD, together with the development of new techniques, will help in identifying and considering risk factors that trigger the onset and progression of the condition in each patient, enabling us to design a personalised clinical approach that will lead to more effective clinical therapies.

The heterogeneity of PD represents a challenge for therapeutic development, which makes it extremely important to accomplish two essential objectives: to identify early biomarkers that can be detected before neurodegeneration manifests, and to design disease-modifying therapies that may be used in patients diagnosed using these biomarkers, so that the condition may be treated before it is too late.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2021.07.006.

References

1. Smart I, Leblond CP. Evidence for division and transformations of neuroglia cells in the mouse brain, as derived from radioautography after injection of thymidine-H3. J Comp Neurol. 1961;116:349–67.
2. Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol. 1965;124:319–35.
3. Kaplan MS, Hinds JW. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. Science. 1977;197:1092–4.
4. Goldman SA, Nottebohm FP. Neuronal production, migration, and differentiation in a vocal control nucleus of the adult female canary brain. Proc Natl Acad Sci U S A. 1983;80:2390–4.
5. Boldrini M, Fulmore CA, Tartt AN, Simeon LR, Pavlova I, Poposka V, Rosoklija GB, Stankov A, Arango V, Dwork AJ, et al. Human hippocampal neurogenesis persists throughout aging. Cell Stem Cell. 2018;22:589–99 e5.
6. Carradori D, Eyer J, Saulnier P, Préat V, des Riex A. The therapeutic contribution of nanomedicine to treat neurodegenerative diseases via neural stem cell differentiation. Biomaterials. 2017;2017(123):77–91.
7. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol. 2020;27(1):27–42. https://doi.org/10.1111/ene.14108.
8. Liu AK, Chang RC, Pearce RK, Gentleman SM. Nucleus basalis of Meynert revisited: Anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. Acta Neuropathol. 2015;129:527–40.
9. Walden H, Muqit MMK. Ubiquitin and Parkinson's disease through the looking glass of genetics. Biochem J. 2017 Apr 13;474(9):1439–51. https://doi.org/10.1042/BCJ20160498.
10. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci. 1998;95:6469–73. https://doi.org/10.1073/pnas.95.11.6469.
11. Kim TY, Leem E, Lee JM, Kim SR. Control of reactive oxygen species for the prevention of Parkinson's disease: the possible application of flavonoids. Antioxidants. 2020;9:583. https://doi.org/10.3390/antiox9070583.
12. Schapira AHV, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem. 1990;54:823–7. https://doi.org/10.1111/j.1471-4159.1990.tb02325.x.
13. Borsche M, König IR, Delcambre S, Petrucci S, Balck A, Brüggemann N, Zimprich A, Wasner K, Pereira SL, Avenali M, Deuschle C, Badanjak K, Ghelfi J, Gasser T, Kasten M, Rosenstiel P, Lohmann K, Brockmann K, Valente EM, Youle RJ, Grünewald A, Klein C. Mitochondrial damage associated inflammation highlights biomarkers in PRKN/PINK1 parkinsonism. Brain. 2020;143:3041–51. https://doi.org/10.1093/brain/awaa246.
14. Valente EM, Bentivoglio AR, Dixon PH, Ferraris A, Ialongo T, Frontali M, Albanese A, Wood NW. Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. Am J Hum Genet. 2001;68:895–900. https://doi.org/10.1086/319522.
15. Kahle PJ, Neumann M, Ozmen L, Muller V, Jacobsen H, Schindzielorz A, Okochi M, Leimer U, Van Der Putten H, Probst A, et al. Subcellular localization of wild-type and Parkinson's disease-associated mutant alpha -synuclein in human and transgenic mouse brain. J Neurosci. 2000;20:6365–73.
16. Van der Putten H, Wiederhold KH, Probst A, Barbieri S, Mistl C, Danner S, Kauffmann S, Hofele K, Spooren WP, Ruegg MA, et al. Neuropathology in mice expressing human alpha-synuclein. J Neurosci. 2000;20:6021–9.
17. Bezard E, Jaber M, Gonon F, Boireau A, Bloch B, Gross CE. Adaptive changes in the nigrostriatal pathway in response to increased 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurodegeneration in the mouse. Eur J Neurosci. 2000;12:2892–900.
18. Di Monte DA, McCormack A, Petzinger G, Janson AM, Quik M, Langston WJ. Relationship among nigrostriatal denervation,

parkinsonism, and dyskinesias in the MPTP primate model. Mov Disord. 2000;15:459–66.
19. Chen JJ, Swope DM. Pharmacotherapy for Parkinson's disease. Pharmacotherapy. 2007;27(12 Pt 2):161S–73S. https://doi.org/10.1592/phco.27.12part2.161S.
20. Savitt JM, Dawson VL, Dawson TM. Diagnosis and treatment of Parkinson disease: molecules to medicine. J Clin Invest. 2006;116:1744–54. https://doi.org/10.1172/JCI29178.
21. Moriarty N, Parish C, Dowd E. Primary tissue for cellular brain repair in Parkinson's disease: promise, problems and the potential of biomaterials. Eur J Neurosci. 2019;49:472–86.
22. Müller-Rebstein S, Trenkwalder C, Oertel WH, Culmsee C, Eckermann G, Höglinger GU. Pharmacotherapy of Parkinson's disease: aspects of drug safety. Nervenarzt. 2017;88(8):888–94. https://doi.org/10.1007/s00115-017-0345-8.
23. Olaf R. Parkinson's disease: basic knowledge. Med Monatsschr Pharm. 2016 Jul;39(7):277–81.
24. Fox SH, Katzenschlager R, Lim SY, Movement Disorder Society Evidence-Based Medicine Committee, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248–66. https://doi.org/10.1002/mds.27372.
25. Yang X, Zhang Y, Xu H, Luo X, Yu J, Liu J, Chuen-Chung Chang R. Neuroprotection of coenzyme Q10 in neurodegenerative diseases. Curr Top Med Chem. 2016;16(8):858–66. https://doi.org/10.2174/1568026615666150827095252.
26. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: initiation of treatment for Parkinson's disease (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2002;58:11–7.
27. Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2006;66:983–95.
28. Ztaou S, Amalric M. Contribution of cholinergic interneurons to striatal pathophysiology in Parkinson's disease. Neurochem Int. 2019;126:1–10. https://doi.org/10.1016/j.neuint.2019.02.019.
29. Espay AJ, Lang AE. Commonmyths in the use of levodopa in Parkinson disease: when clinical trials misinform clinical practice. JAMA Neurol. 2017;74(6):633–4. https://doi.org/10.1001/jamaneurol.2017.0348.
30. Gray R, Ives N, Rick C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet. 2014;384(9949):1196–205. https://doi.org/10.1016/S0140-6736(14)60683-8.
31. Lee DJ, Lozano AM. The future of surgical treatments for Parkinson's disease. J Parkinsons Dis. 2018;8(s1):S79–83. https://doi.org/10.3233/JPD-181467.
32. Narabayashi H, Okuma T. Procaine-oil blocking of the globus pallidus for the treatment of rigidity and tremor of parkinsonism. Proc Japan Acad. 1953;29:134–7.
33. Hassler R, Riechert T. Indications and localization of stereotactic brain operations. Nervenarzt. 1954;25:441–7.
34. Malek N. Deep brain stimulation in Parkinson's disease. Neurol India. 2019;67(4):968–78. https://doi.org/10.4103/0028-3886.266268.
35. Bartus RT, Weinberg MS, Samulski RJ. Parkinson's disease gene therapy: success by design meets failure by efficacy. Mol Ther. 2014;22:487–97.
36. Bankiewicz KS, Forsayeth J, Eberling JL, Sanchez-Pemaute R, Pivirotto P, Bringas J, et al. Long-term clinical improvement in MPTP-lesioned primates after gene therapy with AA V-hAADC. Mol Ther. 2006;14:564–70.
37. Kordower JH, Emborg ME, Bloch J, Ma SY, Chu Y, Leventhal L, et al. Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. Science. 2000;290:767–73.
38. Kordower JH, Herzog CD, Dass B, Bakay RA, Stansell 3rd J, Gasmi M, et al. Delivery of neurturin by AA V2 (CERE-120)-mediated gene transfer provides structural and functional neuroprotection and neurorestoration in MPTPtreated monkeys. Ann Neurol. 2006;60:706–15.
39. Pardridge WM. Tyrosine hydroxylase replacement in experimental Parkinson's disease with transvascular gene therapy. NeuroRx. 2005;2:129–38.
40. Kaplitt MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA, et al. Safety and tolerability of gene therapy with an adeno-associated virus (AA V) borne GAD gene for Parkinson's disease: an open label, phase I trial. Lancet. 2007;369:2097–105.
41. Kirik D, Georgievska B, Bjorklund A. Localized striatal delivery of GDNF as a treatment for Parkinson disease. Nat Neurosci. 2004;7:105–10.
42. Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws Jr ER, et al. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology. 2003;60:69–73.
43. Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med. 2003;9:589–95.
44. Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann Neurol. 2006;59:459–66.
45. George S, Brundin P. Immunotherapy in Parkinson's disease: micromanaging alpha-synuclein aggregation. J Parkinsons Dis. 2015;5:413–24.
46. Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med. 2001;344:710–9.
47. Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol. 2003;54:403–14.
48. Piccini P, Brooks DJ, Bjorklund A, Gunn RN, Grasby PM, Rimoldi O, et al. Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. Nat Neurosci. 1999;2:1137–40.
49. Piccini P, Lindvall O, Bjorklund A, Brundin P, Hagell P, Ceravolo R, Oertel W, Quinn N, Samuel M, Rehncrona S, et al. Delayed recovery of movement-related cortical function in Parkinson's disease after striatal dopaminergic grafts. Ann Neurol. 2000;48:689–95.
50. Kordower JH, Rosenstein JM, Collier TJ, Burke MA, Chen EY, Li JM, et al. Functional fetal nigral grafts in a patient with Parkinson's disease: chemoanatornic, ultrastructural, and metabolic studies. J Comp Neurol. 1996;370:203–30.
51. Mendez L, Sanchez-Pernaute R, Cooper O, Vinuela A, Ferrari D, Bjorklund L, Dagher A, Isacson O. Cell type analysis of functional fetal dopamine cell suspension transplants in the striatum and substantia nigra of patients with Parkinson's disease. Brain. 2005;128:1498–501.
52. Lindvall O, Bjorklund A. Cell replacement therapy: helping the brain to repair itself. NeuroRx. 2004;1:379–81.
53. Bjorklund A, Dunnett SB, Brundin P, Stoessl AJ, Freed CR, Breeze RE, et al. Neural transplantation for the treatment of Parkinson's disease. Lancet Neurol. 2003;2:437–45.
54. Fricker-Gates RA, Dunnett SB. Rewiring the Parkinsonian brain. Nat Med. 2002;8:105–6.

55. Kordower JH, Sortwell CE. Neuropathology of fetal nigra transplants for Parkinson's disease. Prog Brain Res. 2000;127: 333–44.
56. Yasuhara T, Kameda M, Sasaki T, Tajiri N, Date I. Cell therapy for Parkinson's disease. Cell Transplant. 2017;26:1551–9.
57. Bjorklund A, Lindvall O. Cell replacement therapies for central nervous system disorders. Nat Neurosci. 2000;3:537–44.
58. Hagell P, Schrag A, Piccini P, Jahanshahi M, Brown R, Rehncrona S, et al. Sequential bilateral transplantation in Parkinson's disease: effects of the second graft. Brain. 1999;122:1121–32.
59. Hauser RA, Freeman TB, Snow BJ, Nauert M, Gauger L, Kordower JH, et al. Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease. ArchNeurol. 1999;56:179–87.
60. Lindvall O, Hagell P. Clinical observations after neural transplantation in Parkinson's disease. Prog Brain Res. 2000;127:299–320.
61. Carlsson T, Carta M, Winkler C, Bjorklund A, Kirik D. Serotonin neuron transplants exacerbate L-DOP A-induced dyskinesias in a rat model of Parkinson's disease. J Neurosci. 2007;27:8011–22.
62. Kuan WL, Lin R, Tyers P, Barker RA. The importance of A9 dopaminergic neurons in mediating the functional benefits of fetal ventral mesencephalon transplants and levodopa-induced dyskinesias. Neurobiol Dis. 2007;25:594–608.
63. Piccini P, Pavese N, Hagell P, Reirner J, Bjorklund A, Oertel WH, et al. Factors affecting the clinical outcome after neural transplantation in Parkinson's disease. Brain. 2005;128:2977–86.
64. Freed CR, Breeze RE, Fahn S, Eidelberg D. Preoperative response to levodopa is the best predictor of transplant outcome. Ann Neurol. 2004;55:896.
65. Ramachandran AC, Bartlett LE, Mendez IM. A multiple target neural transplantation strategy for Parkinson's disease. Rev Neurosci. 2002;13:243–56.
66. Arjona V, Minguez-Castellanos A, Montoro RJ, Ortega A, Escamilla F, Toledo-Aral JJ, et al. Autotransplantation of human carotid body cell aggregates for treatment of Parkinson's disease. Neurosurgery. 2003;53:321–8.
67. Minguez-Castellanos A, Escamilla-Sevilla F, Hotton GR, Toledo-Aral O-MA, Mendez-Ferrer S, et al. Carotid body autotransplantation in Parkinson disease: a clinical and positron emission tomography study. J Neurol Neurosurg Psychiatry. 2007;78:825–31.
68. Stover NP, Bakay RA, Subramanian T, Raiser CD, Cornfeldt ML, Schweikert AW, et al. Intrastriatal implantation of human retinal pigment epithelial cells attached to microcarriers in advanced Parkinson disease. Arch Neurol. 2005;62:1833–7.
69. Watts RL, Raiser CD, Stover NP, Comfeldt ML, Schweikert AW, Allen RC, et al. Stereotaxic intrastriatal implantation of human retinal pigment epithelial (hRPE) cells attached to gelatin microcarriers: a potential new cell therapy for Parkinson's disease. J Neural Transm. 2003;65(suppl):215–27.
70. Nam H, Lee KH, Nam DH, et al. Adult human neural stem cell therapeutics: current developmental status and prospect. World J Stem Cells. 2015;7(1):126–36.
71. Herberts CA, Kwa MS, Hermsen HP. Risk factors in the development of stem cell therapy. J Transl Med. 2011;9:29.
72. Kitada M, Dezawa M. Parkinson's disease and mesenchymal stem cells: potential for cell-based therapy. Parkinsons Dis. 2012;2012:873706.
73. Politis M, Lindvall O. Clinical application of stem cell therapy in Parkinson's disease. BMC Med. 2012;10:1.
74. Huang Y, Chang C, Zhang J, et al. Bone marrow-derived mesenchymal stem cells increase dopamine synthesis in the injured striatum. Neural Regen Res. 2012;7(34):2653–62.
75. Zhang Y, Li C, Jiang X, et al. Human placenta-derived mesenchymal progenitor cells support culture expansion of long-term culture-initiating cells from cord blood CD34+ cells. Exp Hematol. 2004;32(7):657–64.
76. Roubelakis MG, Pappa KI, Bitsika V, et al. Molecular and proteomic characterization of human mesenchymal stem cells derived from amniotic fluid: comparison to bone marrow mesenchymal stem cells. Stem Cells Dev. 2007;16(6):931–52.
77. Erices A, Conget P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol. 2000;109(1):235–42.
78. Berg J, Roch M, Altschuler J, et al. Human adipose-derived mesenchymal stem cells improve motor functions and are neuroprotective in the 6-hydroxydopamine-rat model for Parkinson's disease when cultured in monolayer cultures but suppress hippocampal neurogenesis and hippocampal memory function when cultured in spheroids. Stem Cell Rev. 2015;11 (1):133–49.
79. Romieu-Mourez R, Francois M, Boivin MN, et al. Regulation of MHC class II expression and antigen processing in murine and human mesenchymal stromal cells by IFN-gamma, TGF-beta, and cell density. J Immunol. 2007;179(3):1549–58.
80. Schiess M, Suescun J, Doursout MF, Adams C, Green C, Saltarrelli JG, Savitz S, Ellmore TM. Allogeneic bone marrow-derived mesenchymal stem cell safety in idiopathic Parkinson's disease. Mov Disord. 2021 https://doi.org/10.1002/mds.28582.
81. Gage FH. Mammalian neural stem cells. Science. 2000;287 (5457):1433–8.
82. Taupin P, Gage FH. Adult neurogenesis and neural stem cells of the central nervous system in mammals. J Neurosci Res. 2002;69(6):745–9.
83. Deierborg T, Soulet D, Roybon L, et al. Emerging restorative treatments for Parkinson's disease. Prog Neurobiol. 2008;85 (4):407–32.
84. Kempermann G, Kuhn HG, Gage FH. Genetic influence on neurogenesis in the dentate gyrus of adult mice. Proc Natl Acad Sci. 1997;94(19):10409–14.
85. Luo J, Daniels SB, Lennington JB, et al. The aging neurogenic subventricular zone. Aging Cell. 2006;5(2):139–52.
86. Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282(5391):1145–7.
87. Guenther MG, Frampton GM, Soldner F, et al. Chromatin structure and gene expression programs of human embryonic and induced pluripotent stem cells. Cell Stem Cell. 2010;7(2):249–57.
88. Morizane A, Doi D, Kikuchi T, et al. Direct comparison of autologous and allogeneic transplantation of iPSC-derived neural cells in the brain of a non-human primate. Stem Cell Rep. 2013;1(4):283–92.
89. Kikuchi T, Morizane A, Doi D, et al. Survival of human induced pluripotent stem cell-derived midbrain dopaminergic neurons in the brain of a primate model of Parkinson's disease. J Parkinsons Dis. 2011;1(4):395–412.
90. Samata B, Doi D, Nishimura K, et al. Purification of functional human ES and iPSC-derived midbrain dopaminergic progenitors using LRTM1. Nat Commun. 2016;7:13097.
91. Kikuchi T, Morizane A, Doi D, et al. Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature. 2017;548(7669):592–6.
92. Emborg ME, Liu Y, Xi J, et al. Induced pluripotent stem cellderived neural cells survive and mature in the nonhuman primate brain. Cell Rep. 2013;3(3):646–50.
93. Redmond Jr DE, Vinuela A, Kordower JH, et al. Influence of cell preparation and target location on the behavioral recovery after striatal transplantation of fetal dopaminergic neurons in a primate model of Parkinson's disease. Neurobiol Dis. 2008;29(1):103–16.
94. Davis RL, Weintraub H, Lassar AB. Expression of a single transfected cDNA converts fibroblasts to myoblasts. Cell. 1987;51(6):987–1000.

95. Slack JM. Metaplasia and transdifferentiation: from pure biology to the clinic. Nat Rev Mol Cell Biol. 2007;8(5):369–78.
96. Caiazzo M, Dell'Anno MT, Dvoretskova E, et al. Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature. 2011;476(7359):224–7.
97. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science. 1992;255:1707–10.
98. Shetty AK. Progenitor cells from the CA3 region of the embryonic day 19 rat hippocampus generate region-specific neuronal phenotypes in vitro. Hippocampus. 2004;14:595–614.
99. Ostenfeld T, Caldwell MA, Prowse KR, Linskens MH, Jauniaux E, Svendsen CN. Human neural precursor cells express low levels of telomerase in vitro and show diminishing cell proliferation with extensive axonal outgrowth following transplantation. Exp Neurol. 2000;164:215–26.
100. Lee SH, Lumelsky N, Studer L, Auerbach JM, McKay RO. Efficient generation of midbrain and hindbrain neurons from mouse embryonic stem cells. Nat Biotechnol. 2000;18:675–9.
101. Kawasaki H, Hirofumi S, Mizuseki K, Watanabe K, Urano F, Lchinose H, Haruta M, Takahashi M, Yoshikawa K, Nishikawa SI, et al. Generation of dopaminergic neurons and pigmented epithelia from primate ES cells by stromal cell-derived inducing activity. Proc Natl Acad Sci U S A. 2002;99:1580–5.
102. Perrier AL, Tabar V, Barberi T, Rubio ME, Bruses J, Topf N, Harrison NL, Studer L. Derivation of midbrain dopamine neurons from human embryonic stem cells. Proc Natl Acad Sci U S A. 2004;101(34):12543–8.
103. Cibelli JB, Grant KA, Chapman KB, Cunniff K, Worst T, Green HL, Walker SJ, Gutin PH, Vilner L, Tabar V, et al. Parthenogenetic stem cells in nonhuman primates. Science. 2002;295:819.
104. Barberi T, Klivenyi P, Calingasan N, Lee H, Kawamata H, Loonam K, Perrier A, Bruses J, Rubio M, Topf N, et al. Neural subtype specification of fertilization and nuclear transfer embryonic stem cells and application in parkinsonian mice. Nat Biotech. 2003;21:1200–7.
105. Takahashi K, Okita K, Nakagawa M, Yamanaka S. Induction of pluripotent stem cells from fibroblast cultures. Nat Protoc. 2007;2:3081–9.
106. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663–76.
107. Stoddard-Bennett T, Reijo Pera R. Treatment of Parkinson's disease through personalized medicine and induced pluripotent stem cells. Cells. 2019;8(1):26. https://doi.org/10.3390/cells8010026.
108. Bruggeman KF, Moriarty N, Dowd E, Nisbet DR, Parish CL. Harnessing stem cells and biomaterials to promote neural repair. Br J Pharmacol. 2019;176:355–68.
109. Bordoni M, Scarian E, Rey F, Gagliardi S, Carelli S, Pansarasa O, Cereda C. Biomaterials in neurodegenerative disorders: a promising therapeutic approach. Int J Mol Sci. 2020;21:3243. https://doi.org/10.3390/ijms21093243.
110. Villa A, Liste I, Courtois ET, et al. Generation and properties of a new human ventral mesencephalic neural stem cell line. Exp Cell Res. 2009;315(11):1860–74.
111. Ghaleb AM, Nandan MO, Chanchevalap S, et al. Kruppel-like factors 4 and 5: the yin and yang regulators of cellular proliferation. Cell Res. 2005;15(2):92–6.
112. Hochedlinger K, Yamada Y, Beard C, et al. Ectopic expression of Oct-4 blocks progenitor-cell differentiation and causes dysplasia in epithelial tissues. Cell. 2005;121(3):465–77.
113. Park ET, Gum JR, Kakar S, et al. Aberrant expression of SOX2 upregulates MUC5AC gastric foveolar mucin in mucinous cancers of the colorectum and related lesions. Int J Cancer. 2008;122(6):1253–60.
114. Kuttler F, Mai S. c-Myc, genomic instability and disease. Genome Dyn. 2006;1:171–90.
115. Howe SJ, Mansour MR, Schwarzwaelder K, et al. Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. J Clin Invest. 2008;118(9):3143–50.
116. Pfisterer U, Kirkeby A, Torper O, et al. Direct conversion of human fibroblasts to dopaminergic neurons. Proc Natl Acad Sci. 2011;108(25):10343–8.
117. Jellinger KA. Neuropathobiology of non-motor symptoms in Parkinson disease. J Neural Transm. 2015;122:1429–40.
118. Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: time to be precise. Mov Disord. 2017;32:1147–54.
119. Bjorklund A, Stenevi U. Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. Brain Res. 1979;177:555–60.
120. Bjorklund A, Stenevi U, Dunnett SB, Iversen SD. Functional reactivation of the deafferented neostriatum by nigral transplants. Nature. 1981;289:497–9.
121. Dunnett SB, Bjorklund A, Stenevi U, Iversen SD. Behavioural recovery following transplantation of substantia nigra in rats subjected to 6-OHDA lesions of the nigrostriatal pathway. I. Unilateral lesions. Brain Res. 1981;215:147–61.
122. Byers B, Lee HL, Reijo Pera R. Modeling Parkinson's disease using induced pluripotent stem cells. Curr Neurol Neurosci Rep. 2012;12:237–42.
123. Nashun B, Hill PW, Hajkova P. Reprogramming of cell fate: epigenetic memory and the erasure of memories past. EMBO J. 2015;34:1296–308.
124. Phetfong J, Supokawej A, Wattanapanitch M, Kheolamai P, U-Pratya Y, Issaragrisil S. Cell type of origin influences iPSC generation and differentiation to cells of the hematoendothelial lineage. Cell Tissue Res. 2016;365:101–12.
125. Ruetz T, Kaji K. Routes to induced pluripotent stem cells. Curr Opin Genet Dev. 2014;28:38–42.
126. Takahashi K, Yamanaka S. A decade of transcription factor-mediated reprogramming to pluripotency. Nat Rev Mol Cell Biol. 2016;17:183–93.
127. Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Agundez JA. Advances in understanding genomic markers and pharmacogenetics of Parkinson's disease. Expert Opin Drug Metab Toxicol. 2016;12:433–48.
128. Kim HJ, Jeon B. How close are we to individualized medicine for Parkinson's disease? Expert Rev Neurother. 2016;16(7):815–30. https://doi.org/10.1080/14737175.2016.1182021.
129. Zappia M, Annesi G, Nicoletti G, Arabia G, Annesi F, Messina D, Pugliese P, Spadafora P, Tarantino P, Carrideo S, et al. Sex differences in clinical and genetic determinants of levodopa peak-dose dyskinesias in Parkinson disease: an exploratory study. Arch Neurol. 2005;62:601–5.
130. Ghamgosha M, Latifi AM, Meftahi GH, Mohammadi A. Cellular, molecular and non-pharmacological therapeutic advances for the treatment of Parkinson's disease: separating hope from hype. Curr Gene Ther. 2018;18(4):206–24. https://doi.org/10.2174/1566523218666180910163401.