REVIEWS

Therapeutic Applications of Induced Pluripotent Stem Cell Use in Parkinson's Disease Models

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Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder resulting from the loss of particular nigrostriatal dopaminergic (DA) neuron projections. Current treatments only address the symptoms of PD and do not work to repair the causative neurodegeneration. Using both Ovid MEDLINE (n = 10) and Google Scholar (n = 10), we conducted a literature search relevant to treating the underlying causes of this disease with induced pluripotent stem cell (iPSC) therapy. In vitro studies of iPSC lines have demonstrated their ability to model neurodegeneration in DA neurons in addition to specific genetic risk factors, allowing for personalized pharmacological testing and treatment. In vivo studies have progressed over the last decade demonstrating the clinical safety and efficacy of iPSC transplantation in primate and human models. We present research that improves limitations of current methods, such as purification techniques, specific differentiation markers, cryopreservation of iPSCs, and CORIN sorting technology for large-scale production. Due to the evolution and improvement of these methods, we encourage the advancement and expansion of domestic PD-focused iPSC clinical trials.

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disease resulting in the loss of mobility and muscle control. Symptoms include bradykinesia, tremor, rigidity, and postural instability. It is one of the most common neurodegenerative diseases, with an incidence of 60,000 cases per year in the United States alone. PD is a disorder of the extrapyramidal system, which includes motor structures of the basal ganglia, where dopaminergic (DA) neurons from the substantia nigra are lost. DA neurons are extensively arborized, supply millions of synapses, and require a copious energy supply in order to release neurotransmitters along the long length of their mostly unmyelinated axons.¹ Because of this high energy demand, DA neurons are particularly vulnerable to degeneration due to higher rates of mitochondrial oxidative phosphorylation, a smaller reserve capacity, increased density of axonal mitochondria, more complex axonal arborization, and higher levels of basal oxidative stress, ultimately causing patients the associated PD symptoms.^{1,2} With the loss of DA neurons comes inadequate stimulation of the D1 and D2 receptors in the brain. This leads to lack of stimulation of the thalamus, resulting in decreased motor activity characteristic of PD, and of the frontal cortex, which results in problems with executive function. Research focused on DA therapies has indicated that restored D1 and D2 receptor activation improves the motor symptoms of PD.³

PD has also been associated with variations in the *SNCA* gene, which encodes the protein α -synuclein. Overproduction of this protein has been shown to aggregate and form fibrils associated with Lewy bodies, a hallmark of PD. Lewy bodies are defined as intracellular aggregates composed of proteins and lipids and α -synuclein is the principal protein constituent. Lewy bodies have been shown to accumulate in DA neurons, impairing their function and disrupting the neurotransmission of dopamine. Accordingly, *SNCA* gene variations and the α -synuclein protein have been identified as potential targets for PD gene therapy.³ In addition to the *SNCA* gene, the Leucine-rich repeat kinase 2 (*LRRK2*) gene has been connected to PD. *LRRK2* is a kinase responsible for increased activity leading to upregulation of α -synuclein levels in the formation of Lewy bodies.⁴ This gene is linked with high prevalence because it is the most common variation of PD, particularly sporadic PD and autosomal dominant inherited PD.⁵ Research in gene therapies is ongoing. While gene therapy may provide research models, gene therapy cannot restore DA neuron function and, therefore, are not curative in their current state.

Currently, there is no cure for PD and treatment is focused on alleviating symptoms. PD is a heterogeneous disease with a variety of potential underlying variations that are unique to each person's onset and progression timeline. Accordingly, treatment is highly personalized and varies based on severity of disease progression. Carbidopa-levodopa remains the most effective treatment and helps address the diminished dopamine levels in the brain. Other pharmacological therapies include dopamine agonists, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, and anticholinergics. Additional treatments include lifestyle changes, physical therapy, and in some cases, deep brain stimulation.⁶

Induced pluripotent stem cells (iPSCs) have gained traction as another viable option for PD therapy. iPSCs are defined as adult cells that have been genetically reprogrammed to an embryonic stem cell-like state. iPSCs and human embryonic stem cells (hESCs) both share pluripotent capacity with the ability to self-renew and differentiate into cell types from any of the 3 embryonic germ layers, including ectoderm-derived neurons. However, iPSC use is preferred because it is less ethically contested. Unlike the fetal tissue source of hESCs, iPSCs are obtained from skin biopsies to expand fibroblasts. Induced pluripotency is accomplished through forced gene expression and exposure to factors important for maintaining the defining properties of embryonic stem cells.⁷ As a result, iPSCs can differentiate into any tissue type in the body, including DA neurons. Several protocols have already been established to successfully generate DA neurons. Modern protocols provide a viable source of DA neuron generation and establishes iPSCs as an important potential therapy for PD.⁸ This review article defines the timeline of iPSC research and the progress of current clinical trials.

Methods

We conducted literature searches using both Ovid MEDLINE and Google Scholar between April 17, 2020, and April 28, 2020. Articles were chosen based on relevance to iPSC therapy and PD therapy. We selected primary literature that has been recently published to maintain validity of the review. Older articles were included for reference to previous research, background information on the PD process, and the use of iPSCs in various mouse, primate, and human models.

The Ovid MEDLINE keywords used were *induced pluripotent stem cells* exploded using OR and *Parkinson's disease* with subgroup *therapy*. These search terms were combined using AND and limited to English language with year limits from 2017 to present and yielded 35 results. Secondary literature sources, such as meta-analyses and literature reviews, were excluded, which provided us with 23 relevant articles. Furthermore, studies were planned to be excluded if access to the full article could not be obtained, however, no articles were excluded based on this criteria ($n = 0$). Otherwise, all current iPSC research was included in our review. Additional searches including further *Parkinson's disease* subgroups such as *rehabilitation* and *therapeutic use* did not provide any relevant results when combined with *induced pluripotent stem cells*. A final search was conducted using *Parkinson's disease* exploded and *induced pluripotent stem cells* exploded, then combined using AND, and limited to 2010 to the present. When review articles were excluded, this search yielded 78 results. We kept the search terms for *induced pluripotent stem cells* broad to account for in vitro and in vivo mouse, primate, and human models. The *Parkinson's disease* search term was limited to the therapy subheading to confine results relevant to this review article.

We used Google Scholar searches to gather further articles to review. The keywords searched were as follows: *induced pluripotent stem cells*, *Parkinson's disease*, *Parkinson's disease process*, *SNCA gene*, *cell therapy*, and *in vivo*. As with Ovid MEDLINE, search results were limited to 2017 to the present, unless used for background knowledge. Articles were planned to be excluded if they were primary literature, such as review articles, if they were not English-language publications, and if access to the full text of the article was not granted, however, no articles were excluded based on these criteria ($n = 0$).

iPSC Generation

Although mouse and primate models are effective in vivo representations, they struggle to capture the phenotype of human neurological impairments, such as PD, whose etiologies are extraordinarily complex. iPSCs, specifically differentiated into the DA neurons involved in movement control, constitute an accurate in vitro system to model the DA neuron vulnerability. They also serve to demonstrate the fundamental properties of the 2-dimensional (2-D) circuit between neurons. This in vitro system also improves testing of novel PD drugs with improved safety and efficacy. To correctly recapitulate the PD

phenotype, stem cells must be differentiated to the specific implicated subset of ventral midbrain DA neurons. The difficulty of accurately modeling and treating an individual's distinct disease using stem cells is solved by inducing pluripotency of a patient's own adult somatic cells. Resulting iPSCs are both accepted by the host's sensitive immune system and contain the specific PD variations that contribute to the host's individualized disease process.

As previously stated, variations in the *SNCA* gene have been linked to the development of PD. More specifically, multiplications of *SNCA* have been linked to familial PD and variation at the *SNCA* locus has been identified as a significant risk factor for sporadic PD. Although *SNCA* mutations and α -synuclein dysfunction have been established as significant pathogenic events in the development of PD, research is limited by availability of diseased tissue. A 2011 study⁹ produced multiple iPSC lines from patients with *SNCA* triplication and unaffected first-degree relatives. When these cells were differentiated into DA neurons, those from the *SNCA* triplication patient produced 2 times as much α -synuclein as those derived from the unaffected relative. As a result, this iPSC model provides an experimental system that will allow researchers to identify compounds that reduce levels of α -synuclein. Furthermore, this will also provide the opportunity to determine the mechanism behind α -synuclein induced neurodegeneration.⁹ A better understanding of this pathogenesis may expedite methods of treatment development and testing.

A stable DA iPSC phenotype is achieved by expression of FOXA2, TH, and β -tubulin III.¹⁰ FOXA2 and β -tubulin III are central nervous system transcription factors and neuronal markers, respectively. TH is the enzyme of the rate-limiting step (Tyrosine $\rightarrow$ L-DOPA) for catecholamine (dopamine)-producing neurons. To derive these neurons, iPSCs are induced from adult somatic cells, such as fibroblasts, by transduction of retroviruses containing c-Myc, Klf4, Sox2, and Oct4. By using Cre-recombinase excisable viruses, such as doxycycline-inducible lentiviral vectors, researchers were better able to mimic human neurons by eliminating the residual transgene expression in addition to reducing the tumorigenic potential of reactivating the c-Myc oncogene.¹¹ On removal of reprogramming factors, the authors found an overall 80% reduction of deregulated genes.¹¹ These findings further indicate the reduced teratoma risk and the advancement of research. iPSC clones undergo teratoma analysis before use in any clinical setting. For neural induction at the 2-week time point, these iPSCs are exposed to SMAD, TGF β , and BMP4 inhibitors to derive neural progenitor cells (NPCs). NPCs are then exposed to low-dose retinoic acid, high-activity SHH, FGF8a, and WNT1 to yield the final DA phenotype from the ventral neural tube (Figure 1).¹⁰ Additionally, specific genetic mutations can be incorporated into iPSC generation for individualized disease modeling and therapeutic testing. If an adult skin cell contains an

2 G2019S variation in its nucleus, for example, the phenotype of this specific variations will be reflected in the neuron derived from this adult somatic cell with a sequence variation. This particular phenotype includes an accumulation of α -synuclein, increased transcription of stress-related genes, and caspase 3 activation in response to hydrogen peroxide.⁴ Because of the late-onset hallmark of PD due to oxidative stress-related modifications and epigenetic changes, it is crucial for these DA neurons to have a decreased ability to accommodate stress and a loss of dopamine transporter. With these important functional distinctions, they might serve as an accurate model of PD in which novel pharmacological therapeutics could be tested.

The presence or absence of these crucial genetic markers along the progression of iPSC differentiation can be confirmed using immunofluorescence techniques of cell counting, methylation analysis, and reverse transcriptase (RT)-quantitative polymerase chain reaction (qPCR) with cluster analysis. For example, derived iPSCs undergo immunostaining and methylation level analysis for the pluripotent factors of NANOG, SOX2, SSEA4, and OCT4. Immunocytochemistry confirms their presence at high levels, while methylation level analysis confirms their hypomethylation. Because methylation can often suppress transcription in certain regions, hypomethylation of these genes in iPSCs relative to their parental fibroblasts indicates increased transcription regions, decreased specificity, and increased capacity to derive any cell type.¹¹ FOXA2 and PITX3 expression was confirmed to ensure midbrain neurons were derived as opposed to later corticogenesis forebrain neurons, whereas NPC phenotype is confirmed by immunostaining for PLAG1, Nestin, Vimentin, and qPCR expressing elevated Sox1 mRNA.¹² The combination of this research demonstrates that iPSC generation protocols are well established and provide the necessary foundation for PD-specific projects. The development of these specific markers over time has greatly improved the safety and reliability of iPSC generation, possibly indicating the ability for this technology to be instituted in therapy.

iPSCs In Vitro

Once 2-D PD DA neurons derived from patients are successfully differentiated, the efficacy of novel pharmacological therapies and existing techniques can be tested. Because PD only has supportive rather than curative therapies, in vitro iPSC testing could expedite patient access to effective drugs, thereby improving future PD prognosis.

In a 2014 study,¹³ researchers focused on the previously mentioned *LRRK2* variation's capacity to impair mitochondrial function in addition to its effect of increasing the vulnerability of PD-like iPSCs to cell oxidative stress and inflammation. iPSCs with *LRRK2* with a sequence variation were found to have a greater level of mtDNA damage compared with control DA iPSC neurons, thereby indicating the PD phenotype of decreased oxidative

phosphorylation due to mitochondrial impairment.¹³ The mitochondrial genome is more susceptible to damage and cell death from oxidative stress due to its lack of protective histones and its proximity to the reactive oxygen species-producing inner mitochondrial membrane.¹⁴ Because neurons are permanently differentiated postmitotic tissues, this neuronal degeneration is not easily repaired, and the function carried out by the damaged neurons is lost.¹³ Because this defect contributes to PD pathogenesis, genes associated with this defect can be targeted for correction to slow and potentially cure PD progression of symptoms.

Additionally, zinc fingers are protein segments with zinc ions that serve a structural role to maintain the proper 3-D structure and folding of DNA binding domains. They also play a role in nuclease-mediated repair of mutated DNA. G2019S and R1441C missense in *LRRK2* have been linked to the PD phenotype. When these mutations in iPSCs undergo zinc finger-mediated gene correction, immunostaining and PCR indications of mtDNA show the damage is reversed.¹³ This targeted correction of decreased mitochondrial damage translates to decreased neuronal degeneration and, therefore, decreased PD symptoms.

Due to *LRRK2* mutations in PD being the most common mutation in both familial and sporadic types, these treatments are likely to prove effective in individuals with this subset of PD.⁴ The method of culturing individualized iPSC neuronal plates shows promise in the field of targeted treatment to improve the prognosis of PD. Testing novel and proven pharmacological therapies on 2-dimensional iPSC plates to evaluate which drugs improve circuitry and synaptic function is safer and more efficient than testing drugs in sequence directly on the patient. This is an important consideration in a progressive condition such as PD.

In addition to *LRRK2* missense mutations, *SNCA* duplications (particularly triplications) have been shown to manifest as PD, thereby serving as a novel target for gene therapy. DNA methylation at intron 1 of *SNCA* attenuates expression to normal levels. CRISPR-Cas9 technology has been used to hypermethylate *SNCA* intron 1 on in vitro iPSC-derived DA neurons from a patient with PD that contain *SNCA* triplication. Hypermethylation downregulated *SNCA* mRNA expression and reduced PD-related phenotypic expressions such as production of mitochondrial reactive oxygen species and increased viability of the DA neuron.¹⁵ The use of iPSC technology in *SNCA* gene editing demonstrates the value of iPSCs to additional facets of PD research such as CRISPR-Cas9-based gene therapies.

These collected studies highlight the usefulness of using iPSCs in vitro. iPSCs can be successfully generated into DA neurons that are susceptible for neurodegeneration. In these models, adequate portions of transcriptional machinery are preserved to allow for the precise genetic mechanisms of PD to be explored. Simultaneously, specific genetic risk factors and appropriate

drug therapy can be explored, allowing for personalized treatment. With iPSCs established as a useful method for evaluating and treating the genetic components of PD, studies should move to further clinical trials.

iPSCs In Vivo

A 2010 study¹⁶ used a rodent model to establish the efficacy and safety of iPSC transplantation in vivo. DA neurons were derived from iPSCs of adult patients with PD. These DA neurons showed no signs of neurodegeneration and survived for months when transplanted into an unlesioned adult rodent striatum. After long-term survival in unlesioned models, DA neurons were transplanted in 6-OHDA rodents, an established model of PD. In these lesioned rodents, DA neurons survived at high levels and their 16- to 20-week post-transplantation survival was comparable with those confirmed in other studies using engrafted differentiated hESCs or primate ESCs. Furthermore, the mice showed strong arborization and functional effects of PD, such as motor asymmetry, were mediated. Importantly, none of the grafted iPSCs generated in this study showed signs of tumor growth.¹⁶ This study provides evidence that engrafted iPSC-derived DA neurons can have functional effects in rodent PD models and encourages the development of further differentiation protocols. Furthermore, the rodent models showed gradual improvements over time and may have continued to improve over the course of a longer study. This study's success establishes the need for larger scale in vivo studies of iPSCs as a treatment for PD.

Furthermore, a 2011 study¹⁷ established an initial primate model with grafted human DA iPSCs, which even more strongly indicated the clinical relevance of iPSC use for PD in human therapy through transplantation. The primate was treated with the neurotoxin MPTP, which induces a PD-like syndrome in the host. Pre-graft iPSCs were treated with SHH and WNT signaling to create midbrain precursors. A schedule was created to generate, differentiate, and graft the iPSCs into the primate model on specific days. The transplanted human iPSCs functioned as midbrain DA neurons in the primate to reduce symptoms of PD induced by MPTP, demonstrating initial efficacy for human transplantation for treatment. No tumors were formed for over 2 years and only a mild immune response was elicited under continuous immunosuppressive treatment.¹⁷ The results of this study were novel because, previously, it had proven difficult to engraft iPSCs to an animal without overgrowth of neurons, especially in a primate. Immunosuppressants were required because of the potential for universal stem cells to activate an immune response. The presence of a mild immune response demonstrated the progress that would need to be made before beginning treatment in human models.

Past research has not succeeded in longer-term transplantation of in vivo iPSC-derived DA progenitor cells. A 2017 study¹⁸ also used a primate model treated with MPTP to study the effects of DA neuron iPSC grafts. Using score-based and video-based analyses, the primates had a significant increase in

spontaneous movements after transplantation.¹⁸ An additional major question was the viability of iPSCs transplanted from a patient with PD compared with iPSCs transplanted from a healthy adult. The transplanted neurons extended densely into the host striatum whether the iPSCs were taken from patients with PD or healthy adults, indicating the additional future clinical safety and relevance and isografted iPSCs. Consistent with previous research, no teratomas were formed. MRI/PET imaging techniques were used to monitor the expansion and function of the grafted cells to ensure the absence of neuronal overgrowth.¹⁸ The study was performed over 2 years and demonstrated a strong clinical safety indication for transplanted iPSC therapy, as well as more functional evidence of effective clinical treatment possibilities. The ability for patients to use iPSCs from their own body significantly decreases risk of immune-mediated graft rejection and eliminates the need for immunosuppressive therapy after transplantation.

Additionally, a 2016 study¹⁹ discussed the validity, clinical safety, feasibility, and efficacy of transplanting neural precursor cells in human patients with PD. NPCs of DA neurons were generated from differentiated hESCs in aborted fetal samples. Pre-surgery evaluation of human participants was performed using the Unified Parkinson's Disease Rating Scale and was obtained for comparison with post-surgery NPC injection into the striatum. No delivery adverse effects, tumor formation, immune rejection, or graft-induced adverse effects without the use of immunosuppressants were found in the human participants.¹⁹ This specific study is much further reaching than previous studies because it included human participants. The study controlled the additional risk of using hESCs rather than isografted iPSCs with the use of immunosuppressants, which takes the clinical viability in another direction. Ideally, isografted iPSCs would provide patients with the utmost safety and equal efficacy to other forms of stem cells.

In related projects, Kyoto University and the New York State Stem Cell Science program (NYSTEM) have launched phase 1 clinical trials investigating the safety of in vivo iPSC transplantation for patients with PD. The Kyoto trial has also incorporated phase 2 and 3 portions for efficacy and randomization, but NYSTEM must abide by Food and Drug Administration (FDA) regulations of initial phase 1 trials.²⁰ The NYSTEM review article established the roadmap toward FDA approval for in vivo phase 2 and 3 trials after their phase 1 trial.²¹ The scientific knowledge backing iPSC technology is now established in primate models as well as human models and should be moved through further human trials after phase 1 at NYSTEM in the United States. Based on the available international data, phases 2 and 3 should be scheduled to begin, pending the quality of results from NYSTEM.

iPSC Limitations

Despite the optimistic preclinical perspective of iPSC therapy for treating neurodegenerative diseases such as PD, insufficient clinical data exist to fully support its safety and reproducibility. First, to achieve successful cell transplantation, the right neural cell type has to be derived. Previous studies deriving DA neurons from iPSCs with induction markers, such as WNT and SHH, have shown cultures contaminated with neural types irrelevant in PD, namely any marker other than SHH, WNT, TGF, and IGF that may slow differentiation.²² This poses the initial problem in deriving the correct cell type to treat PD.

Another consideration for iPSC therapy is eliminating the risk of tumorigenesis. Mouse models have demonstrated that transplantation of iPSCs can result in teratomas.²³ Due to this risk, different methods have been used to improve the safety of pretransplant cells by eliminating the undifferentiated iPSCs that can lead to teratomas. This is accomplished by using fully differentiated SNpc DA neurons instead of undifferentiated progenitor cells. Tumorigenic risk can also be reduced with proper purification techniques. Currently, many different techniques using alternative markers for DA progenitor cells exist, such as sorting for CORIN⁺, a marker for progenitor DA neurons.¹⁴ Another existing procedure involves limiting the proliferation capacity of cells by shortening the telomere sequence. This would trigger apoptosis in the event of tumorigenesis. However, these shortened telomere sequences have been shown to be less effective in differentiating to non-DA neuronal cells.²⁴ Thus, it would be important to determine the effect on DA neurons and weigh the risks and benefits of shortening the telomere to consider its effectiveness in treating patients with PD.

As previously discussed, there is still debate surrounding which cell stage (floorplate progenitor cells vs an intermediate neuron vs fully differentiated DA neurons) might be the most efficient method in treating PD when using fully differentiated DA neurons. A 2011 study¹⁷ showed that floorplate progenitor cells were able to differentiate into DA neurons efficiently in rodent and primate brains. Another study²⁵ transplanted fully differentiated DA neurons, specifically NCAM⁺CD29^{low}, into non-human primates and showed that these neurons restored motor function as well as increased survival without immunosuppression. These 2 contrasting studies, among others, call the ideal cellular stage of transplantation into question. However, while the stage of transplantation is still being debated, the most current research by Kikuchi et al¹⁸ in 2017 showed a promising method to determine the ideal cell stage for PD transplantation. This method is the aforementioned CORIN sorting technology, in which iPSCs would be differentiated towards floorplate progenitor cells and then sorted for CORIN.¹⁸ It has been shown that the graft was able to survive and mature into DA neurons as well as demonstrate significant motor recovery without tumor formation.¹⁸ Thus, it is now mostly

accepted that the ideal stage for transplantation would be beyond the floorplate progenitor stage, but prior to differentiation into DA neurons. This stage allows for the most efficient and safe transplantation, as well as cell function and survival.

Furthermore, a major deterrent for *in vivo* iPSC transplantation in humans is the difficulty of large-scale production of iPSCs for clinical use. Stem cells are difficult to store for extended periods and often lose activity. A 2017 study²⁶ implanted previously cryopreserved iPSCs into a mouse and primate model and found that they remained effective with lesioned rats, while showing a reversal in functional deficits long-term. No abnormal growths appeared through 6 months after transplantation, and the neuronal grafts retained fiber innervation.²⁶ Scaling iPSCs to large markets using cryopreservation is, therefore, possible. Because iPSCs are both clinically indicated and amenable to large-scale manufacture, it is possible to make this treatment available to all patients with PD. However, although cryopreserved iPSCs can be used, large-scale production of homogeneous cell types have to be created in a reproducible manner prior to cryopreserving cells. As previously mentioned, a currently ongoing clinical trial using neurons derived from iPSCs by CiRA of Kyoto University has overcome this barrier.²⁰ They have achieved this by strictly following current Good Manufacturing Practices standards created by the FDA, specifically using CORIN sorting to purify floorplate progenitor cells that will ultimately differentiate into DA neurons.¹⁸ Although there are limitations in successfully generating and transplanting iPSCs, there is hope that current research will enhance production methods and decrease the risks mentioned to provide a safe and efficacious method for treating PD.

Conclusion

PD is a progressive neurodegenerative disorder that affects particular nigrostriatal DA neuron projections of the brain. Although there are multiple treatment options to address symptoms, there is no cure or treatment that restores neurons.² While some components of human disease can effectively be studied on animal models, animal cerebral evolution differs drastically from that of a human. Due to the complexity of the human brain, animal models cannot accurately capture the phenotype of neurodegenerative disorders such as PD. iPSCs have the ability to be generated into DA neurons and provide a model for both DA neuron vulnerability and the possible treatment avenue.⁵ Patient-derived iPSCs are advantageous because they are readily accepted by a host's immune system and have the ability to capture each patient's unique genotype. This technology thereby provides opportunities for individualized, mutation-targeted models and therapies.

In vitro studies of iPSCs demonstrate their ability to develop personalized treatment for PD. They afford investigators the ability to evaluate DA neurons susceptible to neurodegeneration while also providing the necessary models to investigate specific genetic risk factors and potential treatments. Although

there are limitations in achieving safe and efficacious transplantation in patients with PD, there are many alternative ways to overcome such risks. Methods such as CORIN sorting technology in reducing tumorigenesis and providing a specific neuronal cell type as well as cryopreserving generated iPSCs have shown positive preclinical outcomes. With these alternative ways to improve production of iPSCs and reduce tumorigenesis, there is hope for the success of the current clinical trials.

The clinical trials using iPSC transplantation in living PD models have been ongoing and improving. Over the last decade, the safety and efficacy of iPSCs, as well as large-scale clinical production of iPSCs, have vastly improved to the point of starting human trials in the United States. International clinical trials have already advanced to phase 3 randomized trials. The evidence of efficacy and lack of adverse effects from international studies demonstrates the clinical safety and efficacy of iPSC transplantation for patients with PD. Pending the results of the current phase 1 trial in the United States, in vivo iPSC therapy is poised to have a large impact on empirical treatment of PD. In sum, the ongoing research in this field and the great strides in the last decade put iPSC therapies at the cutting edge of medicine. Future studies must continue to advance the knowledge, processes, and additional benefits of iPSC use, while exploring safety in clinical trials.

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Conflicts of Interest

No conflicts of interest are present.

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