REVIEW

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The application of iPSCs in Parkinson's disease

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The discovery and application of induced pluripotent stem cells (iPSCs) provide a novel treatment modality for diseases, which remain incurable. Particularly, in the treatment of neurodegenerative diseases such as Parkinson's disease (PD), iPSC-technology holds an interesting prospect for replacement therapy. Currently, the prognostic improvement of PD is limited and relies on symptomatic treatment. However, the symptomatic dopamine-replacement therapies lose their long-duration responses, and novel regenerative treatment modalities are needed. Animal models have provided valuable information and identified pathogenic mechanisms underlying PD but the lack of models that recapitulate the complex pathophysiology of the disease postpones further development of novel therapeutics. This review summarizes the possible uses of iPSCs in PD and discusses the future investigations needed for iPSCs as a possible treatment of PD patients.

Key words: Parkinson's disease, induced pluripotent stem cells, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, animal models

INTRODUCTION

The medical research and application of induced pluripotent stem cells (iPSCs) is advancing rapidly. Although iPSCs are potentially applicable in several different fields of medical research and for clinical purposes (Takahashi and Yamanaka, 2006), they have proven to be particularly valuable in the research of neurodegenerative disease research e.g., Parkinson's disease (PD) (Zhu et al., 2019). PD is characterised by the degeneration of the midbrain dopaminergic (mDA) neurons that are essential for voluntary motor control. The replacement of the lost mDA neurons with iPSCs differentiated into mDA progenitors has shown promising potential in re-establishing DA function (Caiazzo et al., 2011; Pfisterer et al., 2011). Moreover, neural biopsies from PD patients are often inaccessible and difficult to obtain in sufficient quantities for *in vitro* studies of the underlying pathology (Gibb and Lees, 1988; Jowaed et al., 2010). Biopsies often represent later disease stages of PD, which complicates the recapitulation of the comprehensive neuropathology of the disease. However, with iPSC-technology, it is possible to generate and culture patient-specific neurons *in vitro* from biopsy specimens and obtain a model system for investigation of e.g., early stages of PD (Devine et al., 2011). Furthermore, the technology provides possibilities for novel drug screening and it advances the field of personalized medicine (Plummer et al., 2019). Since the discovery of iPSCs, which was made by Nobel laureate Professor Shinya Yamanaka (Takahashi and Yamanaka, 2006; Takahashi et al., 2007) more than a decade ago, the technology has advanced significantly. Professor Yamanaka's research has undoubtedly contributed to all fields of science; however, primarily three applications are exceptionally relevant for iPSC-technology. These comprise novel drug development, regenerative therapy and disease modelling. Although the discovery of iPSC-technology has transformed biomedical research and created novel possibilities for cell identi-

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ty manipulation (Scudellari, 2016), challenges are still ahead. This review will address and discuss the current applications of iPSCs and the limitations of iPSCs as a restorative therapy for PD.

Backgrounds

iPSC-technology

iPSCs constitute of a group of reprogrammable pluripotent stem cells (PSCs), which are derived from adult cells. PSCs are undifferentiated and have the unique capacity to divide endlessly and thereby self-renew. Furthermore, PSCs can develop into the three primary germ cell layers of the early embryo (endoderm, ectoderm and mesoderm) and hereby differentiate into all 230 different cell types of the adult human body (Morgani et al., 2018).

In 2006, an adult mouse cell, a fibroblast, was converted into a PSC (Takahashi and Yamanaka, 2006). A year later, the same method was proven possible in humans as well (Takahashi et al., 2007; Yu et al., 2007). The somatic cells were reprogrammed using retroviral vectors to express specific transcription factors, which are active in embryonic stem cells (ESCs) but are suppressed after cell differentiation. The applied transcription factors (Yamanaka factors) were c-Myc, Klf4, Oct3/4 and Sox2 (Takahashi and Yamanaka, 2006). Oct4 and Sox2 are still used to this day, while improved reprogramming circumvented the need for the oncogene c-myc (Miyoshi et al., 2011; Habib et al., 2013). The differentiation process is well monitored and the technology must follow the Guidelines for Stem Cell Research and Clinical Translation (Daley et al., 2016). The survival of the iPSCs depends on various growth factors such as fibroblast growth factor 2 (FGF-2) and the iPSCs are kept in an undifferentiated state due to high tumorgenicity (Yamashita et al., 2011). iPSCs are seeded on specific feeder layers, which aid the iPSC differentiation into e.g., DA neurons (Takahashi and Yamanaka, 2006; Stanslowsky et al., 2014) but direct neuronal conversion of fibroblasts into DA neurons *in vitro* and *in vivo* is possible with only three transcription factors: Asc11, Brn2 and Myt1l (Vierbuchen et al., 2010; Liu et al., 2012, Nakagawa et al., 2014). With the addition of two genes, *Lmxa1* and *FoxA2* (Pfisterer et al., 2011), the converted neurons can be further directed into a DA neuronal fate. This is confirmed by cell expression of the enzyme tyrosine hydroxylase (TH), which is involved in dopamine synthesis (Vermilyea et al., 2017). Fibroblasts can be substituted with peripheral blood cells (PBCs) and converted into DA neurons (Churko et al., 2013; Effenberg et al., 2015). This has its advantages, as it is easier, quicker, cheaper and less invasive to collect as opposed to a skin biopsy for the collection of fibroblasts (Zhou et al., 2015; Okumura et al., 2019). However, the blood cells are sensitive to temperature fluctuations (Baboo et al., 2019) and the patient might suffer from different clotting disorders (Kitchens et al., 2011), which can interfere with the quality of the PBCs. Furthermore, epigenetic markers might transfer from PBCs to the iPSCs and affect the pluripotency potential, that complicate the iPSCs differentiation (Polo et al., 2010). Epigenetic carryover is a general problem with iPSCs and gene reprogramming might be necessary prior to iPSCs application.

Gene reprogramming

Formerly, iPSC lines showed variability although they were derived from the same human donor due to the different genomic sites of integration of the retroviral vectors, which were used to express the reprogramming factors in clonal lines (Kilpinen et al., 2017). The first report of iPSCs revealed approximately 20 integrations per clonal line (Takahashi et al., 2007). However, replacements with non-integrating viral vectors such as adenovirus (Tashiro et al., 2010) or Sendai virus (Fusaki et al., 2009; Tarnawski et al., 2019) or other non-integrated methods e.g., recombinant proteins or Epstein-Barr nuclear antigen-1 (EBNA-1)-based episomal plasmids have been used successfully for reprogramming (Drozd et al., 2015). Additionally, pluripotent cells have been made transgene-free (Kaji et al., 2009). Genetic variations can occur during the reprogramming process itself (reprogramming-induced), in later stages in the prolonged culture (culture-induced) or they might be pre-existing in the parental somatic cells (Gore et al., 2011; Laurent et al., 2011). Additionally, the iPSCs increase growth rate due to adaption and signs of reduced apoptosis. The genetic variability of the clonal lines could influence the neuronal differentiation efficiency of iPSCs and result in inconsistency between disease lines and control lines (Carcamo-Orive et al., 2017; Kilpinen et al., 2017). The genetic variations produce phenotype variations, which are affected by e.g., point mutations, abnormal DNA-methylation including epigenetic memory and duplications with copy number variations (CNV) (DeBoever et al., 2017). The cell lines are karyotyped for chromosomal abnormalities and single nucleotide polymorphisms (SNPs). Small undetected CNVs in iPSC due to low resolution can be detected with comprehensive SNP arrays (Hussein et al., 2011). To address phenotypic variation issues, genome editing can e.g., introduce mutations in healthy iPSC lines or correct mutations in patient-derived iPSC lines (Soldner et al., 2011; Yusa et al., 2011)

to create isogenic clonal lines, which only differ at the changed base(s). Novel, yet established mechanisms to induce these genetic modifications include zinc-finger nucleases, transcription-activator-like effector nucleases and clustered regularly interspaced short palindromic repeats-Cas9 (CRISPR-Cas9) (Calatayud et al., 2019). The CRISPR-Cas9 gene-editing mechanism (Jinek et al., 2012) can introduce specific disease-associated mutations, capacitate specific point homozygous and heterozygous mutations into iPSCs and edit a single gene copy as opposed to both copies (Paquet et al., 2016) to study precise combinations of disease-associated mutations. Furthermore, transgene-free murine leukemia virus-like particles loaded with Cas 9 and single-guide RNA ribonucleoproteins, called Nanoblades, can induce *in vivo* genome-editing. Additionally, Nanoblades have been complexed with donor DNA for a homology-directed repair or programmed with modified Cas9 to mediate transcriptional upregulation of specific genes (Mangeot et al., 2019). Following gene-editing, Cas9 resides in the cell and might cause unexpected off-target mutations *in vivo* (Schaefer et al., 2017). The gene-editing tool is inexpensive and easily accessible but scientific, medical and ethical considerations are necessary to ensure appropriate application (Baltimore et al., 2015).

Parkinson's disease

PD is a progressive neurodegenerative disorder that affects the motor and cognitive system. The aetiology of PD is unknown but the conceptualisation of PD continues to advance (Kalia and Lang, 2015). The disease is presumably caused by both environmental and genetic risk factors and 80% of patients are classified as having idiopathic PD (Simón-Sánchez et al., 2009; Biernacka et al., 2016). Neuropathologically, midbrain dopaminergic (mDA) neurons degenerate predominantly in substantia nigra pars compacta (SNc), which causes dopamine deficiency and leads to movement abnormalities including bradykinesia, resting tremor, rigidity and postural instability. As PD progresses, patients may develop cognitive impairment, depression and dementia (Hely et al., 2008; Pfeiffer et al., 2014). The mean age of PD diagnosis is 57 years and the disorder affects 1% of the population over 65 years of age (Lang and Lozano, 1998). The reason for the degeneration is unknown, but it presumably involves aggregation of the protein α-synuclein, that has undergone misfolding, and accumulates in neurons as Lewy Bodies (Spillantini et al., 1998). The accumulation of α-synuclein has also been detected in glia cells, which indicates that glia cells play a contributing non-cell autonomous role in PD neurodegeneration by inducing an inflammatory response (Wakabayashi et al., 2000). α-synuclein is encoded by the *SNCA*-gene (Devine et al., 2011). *SNCA*-gene mutations as well as *LRRK2*-gene mutations are highly penetrant and can cause autosomal dominant PD (Kessler et al., 2018) and cause early onset PD (Nguyen et al., 2011). Other genes e.g., *PARK2* and *PINK1* presumably play a role in PD development (Kitada et al., 1998; Simón-Sánchez et al., 2009). The genes regulate key cellular processes and protein homeostasis including intracellular protein and membrane trafficking, neurite structure, ubiquitin-proteasome and lysosome-autophagy systems as well as mitochondrial function (Cuervo et al., 2004). Under physiological conditions, α-synuclein improves ATP synthase efficiency and membrane plasticity, however, when the protein aggregates into beta sheet-rich oligomers, a pathological gain-of-function is induced (Ludtmann et al., 2016). A study showed that iPSC-derived neurons with *SNCA*-triplication (SNCA-Tri) generated high levels of α-synuclein aggregates that interacted with the ATP-synthase and increased the probability of the permeability transition pore (PTP) opening leading to neuronal cell death (Ludtmann et al., 2018).

PD treatment is focused on normalizing the dopamine balance in the nigrostriatal system either by inhibiting the cholinergic fiber system, which dominates after the degeneration of the nigrostriatal projections, or, by improving and stimulating the activity of the remaining dopaminergic projections. The latter is currently the most effective and motor symptoms can be successfully reversed by re-establishing striatal dopaminergic neurotransmission with levodopa/carbidopa treatment (Lewitt, 2008). However, long-term levodopa use is associated with on-off fluctuations and hyperkinesia/dyskinesia (Borgkvist et al., 2018) and occur for 50% of the patients after years of levodopa use (Holloway, 2004). Neurosurgical interventions such as deep brain stimulation (DBS) can help maintain and extend the benefits of levodopa (Deuschl et al., 2006). DBS compensates for the electrical discharge caused by dopamine loss in the internal globus pallidus (GPi) or in the subthalamic nucleus (STN) (Saenger et al., 2017). Whilst current treatment might relieve symptoms, the effect is only temporary (Yoo et al., 2018).

The application of iPSCs

The application of iPSCs is valuable in many areas of disease research (Yusa et al., 2011; Kelaini et al., 2018; Zhao et al., 2019). Patient-derived iPSCs have enabled the study of patient-specific disease models (Trilck et al., 2016) which are useful for testing new therapeutic strategies and elucidating unknown pathology of e.g.,

neurodegenerative diseases. The disease models are particularly useful for the study of neurodegenerative diseases such as Huntington's Chorea (The Hd iPsc Consortium 2012), Alzheimer's disease (Shirotani et al., 2017) and PD (Kikuchi et al., 2017b), because the mechanisms behind the disorders are indistinct and only symptomatic treatment is available (Nakano and Tyler, 1971; Deuschl et al., 2006). Cell transplantation therapy is a possible regenerative treatment for neurodegenerative disorders and patient-specific iPSCs are promising for autologous cell transplantation therapy (Wang et al., 2015). Over the past decade, iPSC-technology has advanced with the development of novel techniques and reprogramming strategies for manipulating, modulating and differentiating iPSCs, which has given further insight into to the underlying pathology of neurodegenerative diseases such as PD (Chinta et al., 2018; Kim et al., 2019). The opportunities for iPSCs in PD are illustrated in Fig. 1 and addressed below.

Cellular disease modelling

The use of iPSCs as cellular disease models provide a unique possibility to investigate the underlying neuropathophysiology of PD (Chinta et al., 2018). This is known as the 'disease in a dish' concept. Prior to cellular disease modelling, the identity and safety of the cell lines are verified by investigating their gene expressions. The European Bank for Induced Pluripotent Stem Cells has launched a catalogue consisting of standardized iPSCs for use in disease modelling in 2016 (De Sousa et al., 2017). Reprogrammed somatic cells derived from PD-patients can be differentiated into mDA neurons constituting formerly non-accessible *in vitro* models (Kaji et al., 2009). The reprogrammed human iPSCs (hiPSCs) are disease and patient-specific and possible gene mutations and/or chromosome abnormalities are retained during reprogramming, which is important for the study of genetic mutations *in vitro* (Reinhardt et al., 2013). Genetic mutations can interfere with key cellular processes and cause protein misfolding, lysosome dysfunction and oxidative stress (Flierl et al., 2014; Bogetofte et al., 2019). In a novel study (di Domenico et al., 2019), iPSC-derived astrocytes and DA neurons from PD patients with the *LRRK2* G2019S mutation and healthy controls were generated *in vitro*. The control and patient-specific iPSC-derived DA neurons were co-cultured with either PD astrocytes or healthy astrocytes respectively. When the control DA neurons were co-cultured with the patient-specific iPSC-derived astrocytes, the axons and dendrites were shortened and disintegrated leading to neuronal death. Furthermore, astrocyte-derived α-synuclein accumulation was present. Conversely, healthy astrocytes co-cultured with DA neurons from PD patients, showed axonal and dendritic regeneration. Additionally, α-synuclein was prevented from accumulating, hereby restoring neuronal function. These results suggest the importance of astrocytes in PD pathogenesis and provide a fundament for exploring novel therapeutic strategies aiming to inhibiting the pathogenic crosstalk between DA neurons and astrocytes.

It has been hypothesized, that an imbalance in the ability of glia cells to detoxify increased production of reactive oxygen species (ROS) due to decreased glutathione levels and lack of neuroprotective growth factors such as glial-cell-derived neurotrophic factor (GDNF), may result in neuronal damage and eventually a progressive loss of DA neurons (Chen et al., 2009). Increased oxidative stress also exacerbates α-synuclein accumulation *in vivo* (Scudamore and Ciossek, 2018). Furthermore, age-related phenotypes in iPSCs can be induced in culture by exposure to mitochondrial toxins like rotenone or paraquat that cause uncontrolled oxidative stress (Nguyen et al., 2011; Ambasudhan et al., 2013). Likewise, the protein progerin induces early

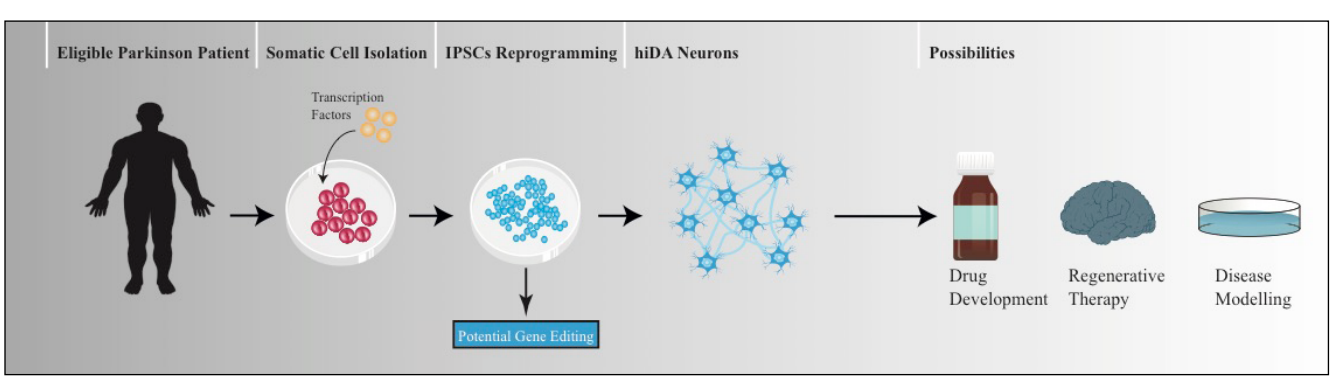

Fig. 1. The possibilities of iPSCs in PD. A skin biopsy is derived from an eligible PD patient. Transcription factors are added to the culture containing cells from the skin biopsy. The cells are reprogrammed into a pluripotent state. Potential gene editing is performed to create human induced dopaminergic neurons before they are used in drug development, regenerative therapy and/or disease modelling.

cellular senescence, which can facilitate ageing *in vitro* (Miller et al., 2013), which is key when modelling a late-onset age-related disease in culture with short preservation. In a recent study (Tagliafierro et al., 2019), hiPSC-derived DA neurons from a patient with *SNCA*-Tri and a healthy control were applied in a PD model *in vitro* using a novel method to intensify neuronal nuclear ageing by passing hiPSCs multiple times at the neural precursor cell stage, before the final differentiation. The patient-specific iPSC-derived DA neurons exhibited advanced nuclear neural ageing compared to the control DA neurons already at the Juvenile stage. The aged hiPSC-derived *SNCA*-Tri neurons contained more α-synuclein aggregates per cell compared to DA neurons at the Juvenile stage. These discoveries are relevant for future drug development and might also be relevant in the use of regenerative therapy to restore DA neurons.

Drug development

The 'disease in a dish' concept also provides *in vitro* models of PD that can be applied for novel drug screening. iPSC-technology provides an adequate number of cells necessary to complete the drug screening and it enables the investigation of several different cell types from the same PD patient (di Domenico et al., 2019). Hereby, iPSCs can be exploited to screen possible novel drugs and simultaneously screen for drug-induced toxicity in the cell cultures (Rane et al., 2018). The most promising drugs are selected for further *in vivo* studies to predict the feasibility of future therapeutics (Carrera et al., 2017; Romero et al., 2017). Therapies aiming at novel targets are needed to develop effective disease modifying treatments for PD (Hsieh et al., 2016). Much research has focused on enhancing the effects of levodopa (Johnston et al., 2018) but sporadic PD is a multifactorial disease and challenging to treat (Langston, 2006). Studies on genetic mutations associated with PD such as *LRRK2* (Schapansky et al., 2018) and *GAB1* (Sidransky and Lopez, 2012) have revealed interesting underlying mechanisms of PD pathogenesis. Furthermore, hiPSCs have been applied to screen and test experimental drugs (Lee et al., 2012; Cao et al., 2016) in cooperation with pharmacological companies. Specifically, addition of the FDA-approved anti-IL-17 antibody to an iPSC-derived midbrain neuron culture from sporadic PD patients rescued DA neuronal death (Sommer et al., 2018). Ultimately, the validation and exploration of drug targets remain a bottle-neck in PD drug discovery. Relevant disease models, which recapitulate the complexity of PD to a greater extent, could further lead to improved drug discovery (Devine et al., 2011). Likewise, relevant animal disease models can be applied to test regenerative therapy such as cell therapy.

Regenerative therapy

The current effects of therapeutic strategies for PD have been incapable of stopping PD progression and restoring DA neural function (Nakano and Tyler, 1971) but cell therapy can potentially accomplish this (Wenning et al., 1997). PD is an interesting target for stem cell-based therapies due to the relatively focal degeneration of mDA neurons. For more than two decades, allografting of fetal ventral mesencephalic tissue has been conducted in clinical trials (Kordower et al., 1997; Li et al., 2016) with various outcomes, ranging from significant improvement to modest or no benefit at all (Lindvall et al., 1989, 1990). This might be explained by lack of standardized fetal tissue, ethical issues associated with its use and post-operative incidences of dyskinesias in a number of patients (Freed et al., 2001; Olanow et al., 2003). iPSC-technology circumvents some of these issues but patient-specific iPSC production is expensive and additional safety issues regarding genetic and epigenetic variations as well as somatic cell use are associated with iPSCs (de Boni et al., 2018). With iPSC-technology, it is possible to use both human leukocyte antigen (Morizane et al., 2017) matched allogeneic (Shiba et al., 2016) and patient-specific autologous cell therapy (Mandai et al., 2017). Formerly, fetal grafts from tissue donors were not matched to the recipients, but the graft-derived dopaminergic innervation was maintained more than two decades after the transplantations (Li et al., 2016) and the indispensable immunosuppressive drugs were applied for less than two years or not at all (Freed et al., 2001; Olanow et al., 2003). Novel studies advocate the use of MHC-matched grafts because MHC-matching improves the engraftment of the iPSC-derived mDA neurons in animal models and reduces the immune response of microglia and lymphocytes. Although autologous transplantation is immunologically ideal, it is time consuming, expensive and not suited for standard therapy (Emborg et al., 2013; Hallett et al., 2015). Genetically, the autologous cells might also carry natural susceptibility to PD. Thus, allogeneic transplantation might prove to be superior to autologous transplantation (Morizane et al., 2017). Direct conversion of a somatic cell into an induced neuron (iN) circumvents safety concerns (Vierbuchen et al., 2010). The iNs are similar to iPSC-derived neurons and can be applied for HLA-matched and patient-specific treatments. Preclinical studies are still needed for the novel technique to elucidate the safety, stability and function of iNs prior to transplantation (Parmar, 2018). However, direct conversion of glia cells

to iN derived from hiPSCs has increasingly gained attention. The method circumvents ethical concerns, risk of tumorigenesis and the need of transplantation to restore DA regeneration in PD (Matsuda et al., 2019).

Animal models

To further advance the preclinical studies, animal models that recapitulate PD better seems imperative as the predictive validity for clinical use and efficiency is based upon the resemblance between the animal models and PD patients (Kin et al., 2019). Ideally, the animal models should resemble human PD in terms of aetiology, pathology and behaviour and combine PD risk factors. Current models focus on aging (Miller et al., 2013), gene transfer (Reinhardt et al., 2013), the initiation of α-synuclein pathology by injection of Lewy Body extracts from PD patients (Recasens et al., 2014) and/or neurotoxins (Thomas et al., 2011) to mimic the disease as close to the human form as possible. Animal models intoxicated with the neurotoxins 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) resemble a parkinsonian state with PD motor symptoms (Alvarez-Fischer et al., 2008; Huang et al., 2017). Reduction of the motor symptoms e.g., tremor and rigidity have been shown in animals after DA stem cell therapy (Kikuchi et al., 2011; Hallett et al., 2015). 6-OHDA and MPTP intoxicated animal models have been a staple in PD research for decades, but the models fail to recapitulate key features of PD such as the accumulation of misfolded α-synuclein. However, the neurotoxin β-sitosterol β-D-glucoside (BSSG) resemblances PD better with several important PD features such as Lewy body-like inclusions, late-stage cognitive effects and pre-motor changes e.g., olfaction in rat models (Van Kampen et al., 2015) and might be preferred when screening for neuroprotective approaches. The BSSG-model has been applied in several studies already (Van Kampen et al., 2014, 2015; Wilson et al., 2002) and is undergoing an independent multi-site validation. Neurotoxins can be combined with genetic modification to mimic PD both genetically and biochemically (Thomas et al., 2011, Vila et al., 2001). Rodent models carrying genetic mutations e.g., *LRRK2* (Nguyen et al., 2011) and *PINK1* (Cooper et al., 2012) underwent patient-specific iPSC autologous cell transplantation but showed higher sensitivity to cellular stressors e.g., oxidative stress than fibroblasts with analogous mutations. However, idiopathic PD-specific iPSC (PDiPSC)-derived mDA neurons survived and functioned in 6-OHDA-lesioned rodent models, which suggests differences between the idiopathic and genetically modified animal models (Kikuchi et al., 2017b).

Cell cultures, rodent and large animal models contribute to deepen the comprehension of PD and the choice of model depends on the specific research question asked. Neurotoxin-lesioned non-human primates (NHPs) imitate humans genomically, neuroanatomically, physiologically and immunogenetically. They exhibit behavioural and symptomatic components of PD closer to the human condition as opposed to rodents, which have fast PD symptom development (Grow et al., 2016; Seo et al., 2019). However, the NHP models are expensive, raise an ethical concern and are therefore not universally allowed. Porcine models circumvent these issues (Glud et al., 2016; Nielsen et al., 2016) and studies have shown promise providing Parkinsonian minipig models (Christensen et al., 2018; Lillethorup et al., 2018a, 2018b). Reduction in striatal DA neurotransmission and loss of TH-positive SN neurons as well as behavioural deficits and microglial activation have been shown. A possible use of the porcine model in regenerative therapy equivalent to the NHP model is presented in Fig. 2. However, porcine model studies lack longevity and further data on the PD pathology development is needed (Bjarkam et al., 2008).

Still, the NHP MPTP model often represents the last animal model of PD research used prior to human clinical trials. A preclinical study (Kikuchi et al., 2017a) using MPTP intoxicated NHPs (*Macaca fascicularis*) implanted with hiPSC-derived DA progenitor cells showed transplant survival after two years with no signs of implant oncogenesis. The progenitor cells functioned as mDA neurons and the mature mDA neurons projected fibers into the striatum of the recipient monkeys. 18F-DOPA PET scans showed increased uptake in the putamen following hiPSC transplantation compared to MPTP-treatment and the recipient monkeys restored spontaneous movements. However, a similar study using MHC-matched iPSC-derived neurons in a HD NHP model, failed to prevent graft rejection (Aron Badin et al., 2019). Furthermore, cell replacement therapy of DA neurons alone might be suboptimal as glia cells are important to PD pathogenesis and DA neuronal death as well (Gu et al., 2010; Zhang et al., 2011). Diseased astrocytes are unable to conduct neurotrophic and –protective functions, which leads to the death of their surrounding neurons. Transplantation of rodent astrocytes overexpressing e.g., GDNF *via* viral vectors in MPTP-intoxicated animal models have shown to induce behavioural recovery and neuroprotection (Drinkut et al., 2012). Likewise, a recent study showed that a viral delivery of GDNF improved graft outcomes of hiPSC-derived cell grafts in a rodent PD model (Gantner et al., 2020). Early exposure to GDNF endorsed survival and plasticity of non-DA neurons which improved the motor recovery in the PD model and delayed exposure to

GDNF enhanced functional recovery *via* improved DA neuronal specification, plasticity and metabolism. Furthermore, it has been hypothesized, that oligodendrocytes and brain myelination play a role in PD pathogenesis (Dean et al., 2016). Studies of the shiverer mouse, which is a hypomyelinating mouse model, have showed myelin formation after transplantation with glial progenitor cells (GPCs) (Windrem et al., 2004, 2008). Furthermore, hiPSC-derived oligodendrocyte progenitor cells (OPCs) have been differentiated into both oligodendrocytes and astrocytes *in vitro* and *in vivo*. The hiPSC-derived progenitor cells were engrafted into shiverer mice and myelinated the hypomyelinated mice successfully and increased their survival with no tumorigenesis nine months post-transplantation (Wang et al., 2013). Another study with the mouse model used both human and mouse glial restricted progenitors (GRPs), that were transplanted into the mice, however, only human GRPs migrated extensively and increased the life span of the dysmyelinated mice (Lyczek et al., 2017). This indicates that transplanted human GPCs might provide therapeutic benefits and that mature myelin might play an additional role in the CNS other than facilitating rapid neuronal conduction. Further studies of large animal models are needed to ensure the potential therapeutic effects in humans.

Clinical use

In 2014, research teams in Japan, USA and Europe created a global consortium, GForce-PD with the aim of cooperatively developing neuronal stem cell therapy for PD. Two clinical trials, CiRA trial and Summit for PD trial, were planned to apply iPSCs as initial cell source while two other human trials would apply hESCs (Fan et al., 2020). To our knowledge, one human clinical trial of allogeneic hiPSC-derived cells is currently ongoing. Based on the promising NHP results (Kikuchi et al., 2017a), the human clinical trial, CiRA, with iPSC-based therapy began in 2018 in Japan (Takahashi, 2019). Seven mid-stage PD patients with a L-DOPA response of > 30%

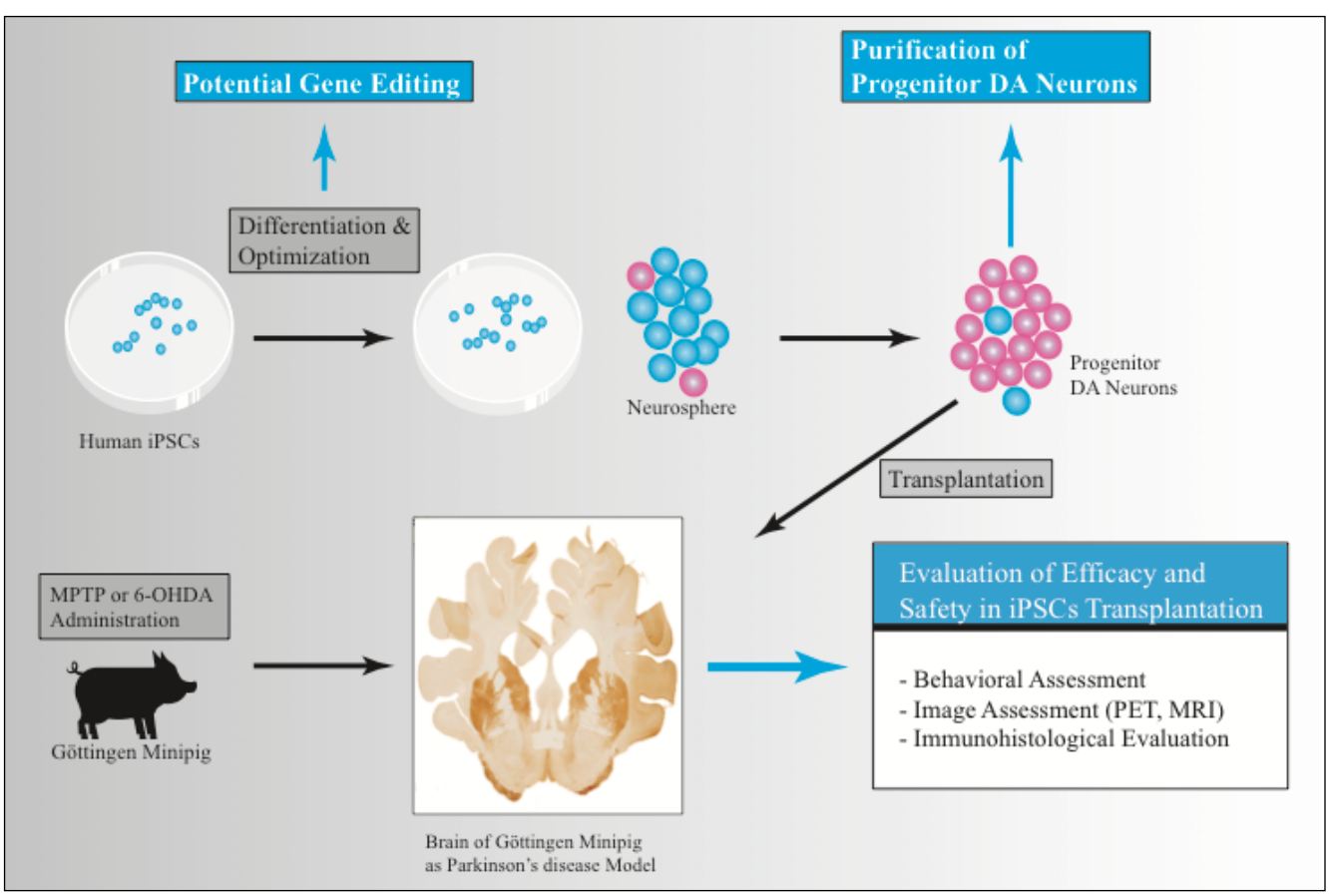

Fig. 2. Parkinson's disease model. The hiPSCs are differentiated into progenitor DA neurons and can then be transplanted into the brain of any disease model subject e.g., the Göttingen minipig. Prior to transplantation, the Göttingen minipig has been intoxicated with MPTP or 6-OHDA to induce a Parkinson-like state. The functionality and safety of the transplantation can then be evaluated using behavioral tests, imaging techniques and immunohistochemical stains for e.g., TH-positive neuron reduction and microglial activation.

were selected for surgical transplantation of 4.8 million allogenic hiPSC-derived DA progenitor cells from an HLA-homozygous donor into the putamen bilaterally *via* stereotaxic brain surgery. The patients were treated with the immunosuppressant drug, Tacrolimus, to avoid rejection of the transplant. So far, no severe adverse events have been reported. The patients are to be followed for at least two years post-transplantation to comprehensively evaluate both qualitative and quantitative outcomes including motor, non-motor, cognitive, psychiatric and quality of life assessments. The graft function and survival, cell proliferation, microglia activation as well as a tumorigenesis are assed *via* MRI and/or [18F]DOPA-PET. The primary end points are tolerability, feasibility and safety with no adverse events. If the trials are successful, efficacy trials will be conducted. The secondary clinical end points are significant improvement of motor and non-motor assessments (Parmar et al., 2020). Additionally, California's Stem Cell Agency (CIRM) has received funding to conduct a clinical trial using autologous cell therapy for PD using patient-specific iPSC-derived DA neurons. The application of autologous stem cells circumvents the use of immunosuppressants (Loring, 2018). Furthermore, gene therapy will be applied to promote GDNF-production to protect DA neurons. However, a novel study with intraputamenal GDNF to PD patients did not show significant clinical improvements against placebo in a randomized controlled trial after 40 weeks although it increased the [18F]DOPA uptake significantly in the putamen (Whone et al., 2019)

CONCLUSIONS

The invention of iPSC-technology has revolutionized the field of stem cell therapy in neurodegenerative disorders such as PD. The iPSCs have improved the possibilities to uncover the aetiology of PD and to identify novel targets for potential medical treatments (di Domenico et al., 2019; Laperle et al., 2020). Furthermore, the iPSCs are a promising source for cell transplantation as opposed to their embryonic counterparts because the iPSCs circumvent the ethical burden associated with the use of embryonic or fetal tissue (Freed et al., 2001; Takahashi and Yamanaka, 2006). The potential of iPSCs is immense, however, issues involved with the application of iPSCs still need to be addressed and resolved. The iPSC-technology should aim to become effective and safe in the reprogramming of the somatic cells in the future (Hu et al., 2010). Less comprehensive and standardized techniques and protocols for differentiation of iPSCs for production of isogenic cell lines are required (Nolbrant et al., 2017). Furthermore, the iPSCs have different origins, genetics, epigenetics and environmental factors, which have to be taken into consideration. Genomic malfunctions have been addressed but not yet perfected (DeBoever et al., 2017), just as full-genome sequencing and epigenomic analyses before application of iPSCs may be needed. As long as it is unknown whether the genetic changes have any functional significance, caution is of great importance particularly in the future clinical application. Although iPSC-derived therapies in PD have been promising in pre-clinical studies, the application of iPSC-technology is still in early stages in the clinical testing and uncertainties remains regarding the readiness for clinical testing and the following potential outcomes. The preclinical study on NHP implanted with hiPSC-derived DA progenitor cells was successful for the 2-year study period, however, other conducted studies with NHPs have not shown the same effect (Aron Badin et al., 2019). The long-term goal is to restore neuronal function in PD patients with hiPSCs. The first human clinical trials using hiPSCs have started in Japan (Takahashi, 2019) but the final results are yet to be published. PD is a complex disease with great individual variability in terms of pathology and progression. Perhaps, there is not one solution that fits all PD-patients and different approaches to treat PD including symptomatic treatment, neuroprotective regimens and cell therapy, may be needed. Nevertheless, it is plausible to think, that iPSC-based cell therapy will play a significant role in the future therapy for PD.

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REFERENCES

Alvarez-Fischer D, Henze C, Strenzke C, Westrich J, Ferger B, Höglinger GU, Oertel WH, Hartmann A (2008) Characterization of the striatal 6-OHDA model of Parkinson's disease in wild type and α-synuclein-deleted mice. Exp Neurol 210: 182–193.

Aron Badin R, Bugi A, Williams S, Vadori M, Michael M, Jan C (2019) MHC matching fails to prevent long-term rejection of iPSC-derived neurons in non-human primates. Nat Comm 10: 4357.

Baboo J, Kilbride P, Delahaye M, Milne S, Fonseca F, Blanco M, Meneghel J, Nancekievill A, Gaddum N, Morris GJ (2019) The impact of varying cooling and thawing rates on the quality of cryopreserved human peripheral blood t cells. Sci Rep 9: 3417.

Baltimore D, Berg P, Botchan M, Carroll D, Charo RA, Church G, Corn JE, Daley GQ, Doudna JA, Fenner M, Greely HT, Jinek M, Martin GS,

Penhoet E, Puck J, Sternberg SH, Weissman JS, Yamamoto KR (2015) A prudent path forward for genomic engineering and germline gene modification. Science 348: 36–38.

Biernacka JM, Chung SJ, Armasu SM, Anderson KS, Lill CM, Bertram L, Ahlskog JE, Brighina L, Frigerio R, Maraganore DM (2016) Genome-wide gene-environment interaction analysis of pesticide exposure and risk of Parkinson's disease. Parkinsonism Relat Disord 32: 25–30.

Bjarkam CR, Nielsen MS, Glud AN, Rosendal F, Mogensen P, Bender D, Doudet D, Møller A, Sørensen JC (2008) Neuromodulation in a minipig MPTP model of Parkinson disease. British J Neurosurgery 22: S9–S12.

Bogetofte H, Jensen P, Ryding M, Schmidt SI, Okarmus J, Ritter L, Worm CS, Hohnholt MC, Azevedo C, Roybon L, Bak LK, Waagepetersen H, Ryan BJ, Wade-Martins R, Larsen MR, Meyer M (2019) PARK(2 mutation causes metabolic disturbances and impaired survival of human iPSC-derived neurons. Front Cell Neurosci 13: 297.

Borgkvist A, Lieberman OJ, Sulzer D (2018) Synaptic plasticity may underlie L-DOPA induced dyskinesia. Curr Opinion Neurobiol 48: 71–78.

Caiazzo M, Dell'Anno MT, Dvoretskova E, Lazarevic D, Taverna S, Leo D, Sotnikova TD, Menegon A, Roncaglia P, Colciago G, Russo G, Carninci P, Pezzoli G, Gainetdinov RR, Gustincich S, Dityatev A, Broccoli V (2011) Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature 476: 224–227.

Calatayud C, Carola G, Fernández-Carasa I, Valtorta M, Jiménez-Delgado S, Díaz M, Soriano-Fradera J, Cappelletti G, García-Sancho J, Raya Á, Consiglio A (2019) CRISPR/Cas9-mediated generation of a tyrosine hydroxylase reporter iPSC line for live imaging and isolation of dopaminergic neurons. Sci Rep 9: 6811.

Cao L, McDonnell A, Nitzsche A, Alexandrou A, Saintot PP, Loucif AJC, Brown AR, Young G, Mis M, Randall A, Waxman SG, Stanley P, Kirby S, Tarabar S, Gutteridge A, Butt R, McKernan RM, Whiting P, Ali Z, Bilsland J, Stevens EB (2016) Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia. Science Translational Medicine 8: 335ra356–335ra356.

Carcamo-Orive I, Hoffman GE, Cundiff P, Beckmann ND, Souza SLD, Knowles JW, Patel A, Papatsenko D, Abbasi F, Reaven GM, Whalen S, Lee P, Shahbazi M, Henrion MYR, Zhu K, Wang S, Roussos P, Schadt EE, Pandey G, Chang R, Quertermous T, Lemischka I (2017) Analysis of transcriptional variability in a large human ipsc library reveals genetic and non-genetic determinants of heterogeneity. Cell Stem Cell 20: 518–532.

Carrera I, Fernandez-Novoa L, Sampedro C, Cacabelos R (2017) Neuroprotective Effect of atremorine in an experimental model of Parkinson's disease. Curr Pharm Des 23: 2673–2684.

Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, Johnson JA (2009) Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: Critical role for the astrocyte. Proc Natl Acad Sci U S A 106: 2933–2938.

Chinta SJ, Woods G, Demaria M, Rane A, Zou Y, McQuade A, Rajagopalan S, Limbad C, Madden DT, Campisi J, Andersen JK (2018) Cellular Senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. Cell Rep 22: 930–940.

Christensen AB, Sørensen JCH, Ettrup KS, Orlowski D, Bjarkam CR (2018) Pirouetting pigs: A large non-primate animal model based on unilateral 6-hydroxydopamine lesioning of the nigrostriatal pathway. Brain Research Bulletin 139: 167–173.

Churko JM, Burridge PW, Wu JC (2013) Generation of human iPSCs from human peripheral blood mononuclear cells using non-integrative sendai virus in chemically defined conditions. Methods Molecular Biol 1036: 81–88.

Cooper O, Seo H, Andrabi S, Guardia-Laguarta C, Graziotto J, Sundberg M, McLean JR, Carrillo-Reid L, Xie Z, Osborn T, Hargus G, Deleidi M, Lawson T, Bogetofte H, Perez-Torres E, Clark L, Moskowitz C, Mazzulli J, Chen L, Volpicelli-Daley L, Romero N, Jiang H, Uitti RJ, Huang Z, Opala G, Scarffe LA, Dawson VL, Klein C, Feng J, Ross OA, Trojanowski JQ, Lee VMY, Marder K, Surmeier DJ, Wszolek ZK, Przedborski S, Krainc D, Dawson TM, Isacson O (2012) Pharmacological rescue of mitochondrial deficits in iPSC-derived neural cells from patients with familial Parkinson's disease. Science Translational Medicine 4: 141ra90.

Cuervo AM, Stafanis L, Fredenburg R, Lansbury PT, Sulzer D (2004) Impaired degradation of mutant α-synuclein by chaperone-mediated autophagy. Science 305: 1292–1295.

Daley GQ, Hyun I, Apperley JF, Barker RA, Benvenisty N, Bredenoord AL, Breuer CK, Caulfield T, Cedars MI, Frey-Vasconcells J, Heslop HE, Jin Y, Lee RT, McCabe C, Munsie M, Murry CE, Piantadosi S, Rao M, Rooke HM, Sipp D, Studer L, Sugarman J, Takahashi M, Zimmerman M, Kimmelman J (2016) Setting global standards for stem cell research and clinical translation: The 2016 ISSCR Guidelines. Stem Cell Rep 6: 787–797.

de Boni L, Gasparoni G, Haubenreich C, Tierling S, Schmitt I, Peitz M, Koch P, Walter J, Wüllner U, Brüstle O (2018) DNA methylation alterations in iPSC- and hESC-derived neurons: potential implications for neurological disease modeling. Clinical Epigenetics 10: 13.

De Sousa PA, Steeg R, Wachter E, Bruce K, King J, Hoeve M, Khadun S, McConnachie G, Holder J, Kurtz A, Seltmann S, Dewender J, Reimann S, Stacey G, O'Shea O, Chapman C, Healy L, Zimmermann H, Bolton B, Rawat T, Atkin I, Veiga A, Kuebler B, Serano BM, Saric T, Hescheler J, Brüstle O, Peitz M, Thiele C, Geijsen N, Holst B, Clausen C, Lako M, Armstrong L, Gupta SK, Kvist AJ, Hicks R, Jonebring A, Brolén G, Ebneth A, Cabrera-Socorro A, Foerch P, Geraerts M, Stummann TC, Harmon S, George C, Streeter I, Clarke L, Parkinson H, Harrison PW, Faulconbridge A, Cherubin L, Burdett T, Trigueros C, Patel M, Lucas C, Hardy B, Predan R, Dokler J, Brajnik M, Keminer O, Pless O, Gribbon P, Claussen C, Ringwald A, Kreisel B, Courtney A, Allsopp TE (2017) Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC) - the Hot Start experience. Stem Cell Research 20: 105–114.

Dean DC, 3rd, Sojkova J, Hurley S, Kecskemeti S, Okonkwo O, Bendlin BB, Theisen F, Johnson SC, Alexander AL, Gallagher CL (2016) Alterations of myelin content in Parkinson's disease: A Cross-Sectional Neuroimaging Study. PLoS ONE 11: e0163774.

DeBoever C, Li H, Jakubosky D, Benaglio P, Reyna J, Olson KM, Huang H, Biggs W, Sandoval E, D'Antonio M, Jepsen K, Matsui H, Arias A, Ren B, Nariai N, Smith EN, D'Antonio-Chronowska A, Farley EK, Frazer KA (2017) Large-scale profiling reveals the influence of genetic Variation on gene expression in human induced pluripotent stem cells. Cell Stem Cell 20: 533–546.

Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, Daniels C, Deutschlander A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenzl S, Mehdorn HM, Moringlane JR, Oertel W, Pinsker MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 355: 896–908.

Devine MJ, Ryten M, Vodicka P, Thomson AJ, Burdon T, Houlden H, Cavaleri F, Nagano M, Drummond NJ, Taanman JW, Schapira AH, Gwinn K, Hardy J, Lewis PA, Kunath T (2011) Parkinson's disease induced pluripotent stem cells with triplication of the α-synuclein locus. Nature Communications 2: 440.

di Domenico, Carola G, Calatayud C, Pons-Espinal M, Muñoz JP, Richaud-Patin Y, Fernandez-Carasa I, Gut M, Faella A, Parameswaran J, Soriano J, Ferrer I, Tolosa E, Zorzano A, Cuervo AM, Raya A, Consiglio A (2019) Patient-Specific iPSC-Derived Astrocytes Contribute to Non-Cell-Autonomous Neurodegeneration in Parkinson's Disease. Stem cell reports 12: 213–229.

Drinkut A, Tereshchenko Y, Schulz JB, Bähr M, Kügler S (2012) Efficient gene therapy for Parkinson's disease using astrocytes as hosts for localized neurotrophic factor delivery. Mol Ther 20: 534–543.

Drozd AM, Walczak MP, Piaskowski S, Stoczynska-Fidelus E, Rieske P, Grzela DP (2015) Generation of human iPSCs from cells of fibroblastic and epithelial origin by means of the oriP/EBNA-1 episomal reprogramming system. Stem Cell Res Ther 6: 122.

Effenberg A, Stanslowsky N, Klein A, Wesemann M, Haase A, Martin U, Dengler R, Grothe C, Ratzka A, Wegner F (2015) Striatal transplantation of human dopaminergic neurons differentiated from induced pluripotent stem cells derived from umbilical cord blood using lentiviral reprogramming. Cell Transplantat 24: 2099–2112.

Emborg ME, Liu Y, Xi J, Zhang X, Yin Y, Lu J, Joers V, Swanson C, Holden JE, Zhang SC (2013) Induced pluripotent stem cell-derived neural cells survive and mature in the nonhuman primate brain. Cell Reports 3: 646–650.

Fan Y, Winanto, Ng SY (2020) Replacing what's lost: a new era of stem cell therapy for Parkinson's disease. Translat Neurodegenerat 9: 2.

Flierl A, Oliveira LM, Falomir-Lockhart LJ, Mak SK, Hesley J, Soldner F, Arndt-Jovin DJ, Jaenisch R, Langston JW, Jovin TM, Schule B (2014) Higher vulnerability and stress sensitivity of neuronal precursor cells carrying an alpha-synuclein gene triplication. PLoS One 9: e112413.

Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S (2001) Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. N Engl J Med 344: 710–719.

Fusaki N, Ban H, Nishiyama A, Saeki K, Hasegawa M (2009) Efficient induction of transgene-free human pluripotent stem cells using a vector based on Sendai virus, an RNA virus that does not integrate into the host genome. Proc Jpn Acad Ser B Phys Biol Sci 85: 348–362.

Gantner CW, de Luzy IR, Kauhausen JA, Moriarty N, Niclis JC, Bye CR, Penna V, Hunt CPJ, Ermine CM, Pouton CW, Kirik D, Thompson LH, Parish CL (2020) Viral delivery of GDNF promotes functional integration of human stem cell grafts in Parkinson's disease. Cell Stem Cell 26: 511–526.

Gibb WR, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51: 745–752.

Glud AN, Bjarkam CR, Azimi N, Johe K, Sorensen JC, Cunningham M (2016) Feasibility of three-dimensional placement of human therapeutic stem cells using the intracerebral microinjection instrument. Neuromodulation 19: 708–716.

Gore A, Li Z, Fung HL, Young JE, Agarwal S, Antosiewicz-Bourget J, Canto I, Giorgetti A, Israel MA, Kiskinis E, Lee JH, Loh YH, Manos PD, Montserrat N, Panopoulos AD, Ruiz S, Wilbert ML, Yu J, Kirkness EF, Belmonte JCI, Rossi DJ, Thomson JA, Eggan K, Daley GQ, Goldstein LSB, Zhang K (2011) Somatic coding mutations in human induced pluripotent stem cells. Nature 471: 63–67.

Grow DA, McCarrey JR, Navara CS (2016) Advantages of nonhuman primates as preclinical models for evaluating stem cell-based therapies for Parkinson's disease. Stem Cell Research 17: 352–366.

Gu XL, Long CX, Sun L, Xie C, Lin X, Cai H (2010) Astrocytic expression of Parkinson's disease-related A53T alpha-synuclein causes neurodegeneration in mice. Mol Brain 3: 12.

Habib O, Habib G, Choi HW, Hong KS, Tae Do J, Moon SH, Chung HM (2013) An improved method for the derivation of high quality iPSCs in the absence of c-Myc. Exp Cell Res 319: 3190–3200.

Hallett PJ, Deleidi M, Astradsson A, Smith GA, Cooper O, Osborn TM, Sundberg M, Moore MA, Perez-Torres E, Brownell AL, Schumacher JM, Spealman RD, Isacson O (2015) Successful function of autologous iPSC-derived dopamine neurons following transplantation in a non-human primate model of Parkinson's disease. Cell Stem Cell 16: 269–274.

Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL (2008) The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord 23: 837–844.

Holloway RG (2004) Pramipexole *vs.* levodopa as initial treatment for Parkinson disease: A 4-year randomized controlled trial. Arch Neurol 61: 1044–1053.

Hsieh C-H, Shaltouki A, Gonzalez AE, Bettencourt da Cruz A, Burbulla LF, St. Lawrence E, Schüle B, Krainc D, Palmer TD, Wang X (2016) Functional Impairment in Miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. Cell Stem Cell 19: 709–724.

Hu BY, Weick JP, Yu J, Ma L-X, Zhang XQ, Thomson JA, Zhang SC (2010) Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency. Proc Natl Acad Sci USA 107: 4335–4340.

Huang D, Xu J, Wang J, Tong J, Bai X, Li H, Wang Z, Huang Y, Wu Y, Yu M, Huang F (2017) Dynamic changes in the nigrostriatal pathway in the MPTP mouse model of Parkinson's disease. Parkinson's Disease 2017: 9349487.

Hussein SM, Batada NN, Vuoristo S, Ching RW, Autio R, Närvä E, Ng S, Sourour M, Hämäläinen R, Olsson C, Lundin K, Mikkola M, Trokovic R, Peitz M, Brüstle O, Bazett-Jones DP, Alitalo K, Lahesmaa R, Nagy A, Otonkoski T (2011) Copy number variation and selection during reprogramming to pluripotency. Nature 471: 58–62.

Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E (2012) A Programmable Dual-RNA–Guided DNA endonuclease in adaptive bacterial immunity. Science 337: 816–821.

Johnston TH, Versi E, Howson PA, Ravenscroft P, Fox SH, Hill MP, Reidenberg BE, Corey R, Brotchie JM (2018) DPI-289, a novel mixed delta opioid agonist / mu opioid antagonist (DAMA), has L-DOPA-sparing potential in Parkinson's disease. Neuropharmacology 131: 116–127.

Jowaed A, Schmitt I, Kaut O, Wüllner U (2010) Methylation regulates alpha-synuclein expression and is decreased in Parkinson's disease patients' brains. J Neurosci 30: 6355–6359.

Kaji K, Norrby K, Paca A, Mileikovsky M, Mohseni P, Woltjen K (2009) Virus-free induction of pluripotency and subsequent excision of reprogramming factors. Nature 458: 771–775.

Kalia LV, Lang AE (2015) Parkinson's disease. Lancet 386: 896–912.

Kelaini S, Vilà-González M, Caines R, Campbell D, Eleftheriadou M, Tsifaki M, Magee C, Cochrane A, O'Neill K, Yang C, Stitt AW, Zeng L, Grieve DJ, Margariti A (2018) Follistatin-like 3 enhances the function of endothelial cells derived from pluripotent stem cells by facilitating β-catenin nuclear translocation through inhibition of glycogen synthase kinase-3β activity. Stem Cells 36: 1033–1044.

Kessler C, Atasu B, Hanagasi H, Simón-Sánchez J, Hauser AK, Pak M, Bilgic B, Erginel-Unaltuna N, Gurvit H, Gasser T, Lohmann E (2018) Role of LRRK2 and SNCA in autosomal dominant Parkinson's disease in Turkey. Parkinsonism Related Disorders 48: 34–39.

Kikuchi T, Morizane A, Doi D, Magotani H, Onoe H, Hayashi T, Mizuma H, Takara S, Takahashi R, Inoue H, Morita S, Yamamoto M, Okita K, Nakagawa M, Parmar M, Takahashi J (2017a) Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model. Nature 548: 592–596.

Kikuchi T, Morizane A, Doi D, Okita K, Nakagawa M, Yamakado H, Inoue H, Takahashi R, Takahashi J (2017b) Idiopathic Parkinson's disease patient-derived induced pluripotent stem cells function as midbrain dopaminergic neurons in rodent brains. J Neurosci Res 95: 1829–1837.

Kikuchi T, Morizane A, Doi D, Onoe H, Hayashi T, Kawasaki T, Saiki H, Miyamoto S, Takahashi J (2011) Survival of human induced pluripotent stem cell-derived midbrain dopaminergic neurons in the brain of a primate model of Parkinson's disease. J Parkinson's Disease 1: 395–412.

Kilpinen H, Goncalves A, Leha A, Afzal V, Alasoo K, Ashford S, Bala S, Bensaddek D, Casale FP, Culley OJ, Danecek P, Faulconbridge A, Harrison PW, Kathuria A, McCarthy D, McCarthy SA, Meleckyte R, Memari Y, Moens N, Soares F, Mann A, Streeter I, Agu CA, Alderton A, Nelson R, Harper S, Patel M, White A, Patel SR, Clarke L, Halai R, Kirton CM, Kolb-Kokocinski A, Beales P, Birney E, Danovi D, Lamond AI, Ouwehand WH, Vallier L, Watt FM, Durbin R, Stegle O, Gaffney DJ (2017) Common genetic variation drives molecular heterogeneity in human iPSCs. Nature 546: 370–375.

Kim H, Park HJ, Choi H, Chang Y, Park H, Shin J, Kim J, Lengner CJ, Lee YK, Kim J (2019) Modeling G2019S-LRRK2 sporadic Parkinson's disease in 3D midbrain organoids. Stem Cell Rep 12: 518–531.

Kin K, Yasuhara T, Kameda M, Date I (2019) Animal models for Parkinson's disease research: Trends in the 2000s. Int J Mol Sci 20: 5402.

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 392: 605–608.

Kitchens CS, Erkan D, Brando LR, Hahn S, James AH, Kulkarni R, Pericak-Vance M, Vance J, Ortel TL (2011) Thrombotic storm revisited: Preliminary diagnostic criteria suggested by the thrombotic storm study group. Am J Med 124: 290–296.

Kordower JH, Styren S, Clarke M, Dekosky ST, Olanow CW, Freeman TB (1997) Fetal grafting for Parkinson's disease: Expression of immune markers in two patients with functional fetal nigral implants. Cell Transplant 6: 213–219.

Lang AE, Lozano AM (1998) Parkinson's Disease. N Engl J Med 339: 1044–1053.

Langston JW (2006) The Parkinson's complex: Parkinsonism is just the tip of the Iceberg. Ann Neurol 59: 591–596.

Laperle AH, Sances S, Yucer N, Dardov VJ, Garcia VJ, Ho R, Fulton AN, Jones MR, Roxas KM, Avalos P, West D, Banuelos MG, Shu Z, Murali R, Maidment NT, Van Eyk JE, Tagliati M, Svendsen CN (2020) iPSC modeling of young-onset Parkinson's disease reveals a molecular signature of disease and novel therapeutic candidates. Nat Med 26: 289–299.

Laurent LC, Ulitsky I, Slavin I, Tran H, Schork A, Morey R, Lynch C, Harness JV, Lee S, Barrero MJ, Ku S, Martynova M, Semechkin R, Galat V, Gottesfeld J, Izpisua Belmonte JC, Murry C, Keirstead HS, Park HS, Schmidt U, Laslett AL, Muller FJ, Nievergelt CM, Shamir R, Loring JF (2011) Dynamic changes in the copy number of pluripotency and cell proliferation genes in human ESCs and iPSCs during reprogramming and time in culture. Cell Stem Cell 8: 106–118.

Lee G, Ramirez CN, Kim H, Zeltner N, Liu B, Radu C, Bhinder B, Kim YJ, Choi IY, Mukherjee-Clavin B, Djaballah H, Studer L (2012) Large-scale screening using familial dysautonomia induced pluripotent stem cells identifies compounds that rescue IKBKAP expression. Nat Biotech 30: 1244–1248.

Lewitt PA (2008) Levodopa for the treatment of Parkinson's disease. N Engl J Med 359: 2468–2476.

Li W, Englund E, Widner H, Mattsson B, Van Westen D, Lätt J, Rehncrona S, Brundin P, Björklund A, Lindvall O, Li JY (2016) Extensive graft-derived dopaminergic innervation is maintained 24 years after transplantation in the degenerating parkinsonian brain. Proc Natl Acad Sci USA 113: 6544–6549.

Lillethorup TP, Glud AN, Alstrup AKO, Mikkelsen TW, Nielsen EH, Zaer H, Doudet DJ, Brooks DJ, Sørensen JCH, Orlowski D, Landau AM (2018a) Nigrostriatal proteasome inhibition impairs dopamine neurotransmission and motor function in minipigs. Exp Neurol 303: 142–152.

Lillethorup TP, Glud AN, Alstrup AKO, Noer O, Nielsen EHT, Schacht AC, Landeck N, Kirik D, Orlowski D, Sorensen JCH, Doudet DJ, Landau AM (2018b) Longitudinal monoaminergic PET imaging of chronic proteasome inhibition in minipigs. Sci Rep 8: 15715.

Lindvall O, Brundin P, Widner H, Rehncrona S, Gustavii B, Frackowiak R, Leenders K, Sawle G, Rothwell J, Marsden C (1990) Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science 247: 574–577.

Lindvall O, Rehncrona S, Brundin P, Gustavii B, Astedt B, Widner H, Lindholm T, Björklund A, Leenders KL, Rothwell JC, Frackowiak R, Marsden D, Johnels B, Steg G, Freedman R, Hoffer BJ, Seiger A, Bygdeman M, Strömberg I, Olson L (1989) Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease: A detailed account of methodology and a 6-month follow-up. Arch Neurol 46: 615–631.

Liu X, Li F, Stubblefield EA, Blanchard B, Richards TL, Larson GA, He Y, Huang Q, Tan AC, Zhang D, Benke TA, Sladek JR, Zahniser NR, Li CY (2012) Direct reprogramming of human fibroblasts into dopaminergic neuron-like cells. Cell Research 22: 321–332.

Loring JF (2018) Autologous induced pluripotent stem cell-derived neurons to treat Parkinson's disease. Stem Cells Dev 27: 958–959.

Ludtmann MHR, Angelova PR, Horrocks MH, Choi ML, Rodrigues M, Baev AY, Berezhnov AV, Yao Z, Little D, Banushi B, Al-Menhali AS, Ranasinghe RT, Whiten DR, Yapom R, Dolt KS, Devine MJ, Gissen P, Kunath T, Jaganjac M, Pavlov EV, Klenerman D, Abramov AY, Gandhi S (2018) α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson's disease. Nat Comm 9: 2293.

Ludtmann MHR, Angelova PR, Ninkina NN, Gandhi S, Buchman VL, Abramov AY (2016) Monomeric alpha-synuclein exerts a physiological role on brain ATP synthase. J Neurosci 36: 10510–10521.

Lyczek A, Arnold A, Zhang J, Campanelli JT, Janowski M, Bulte JWM, Walczak P (2017) Transplanted human glial-restricted progenitors can rescue the survival of dysmyelinated mice independent of the production of mature, compact myelin. Exp Neurol 291: 74–86.

Mandai M, Watanabe A, Kurimoto Y, Hirami Y, Morinaga C, Daimon T, Fujihara M, Akimaru H, Sakai N, Shibata Y, Terada M, Nomiya Y, Tanishima S, Nakamura M, Kamao H, Sugita S, Onishi A, Ito T, Fujita K, Kawamata S, Go MJ, Shinohara C, Hata K, Sawada M, Yamamoto M, Ohta S, Ohara Y, Yoshida K, Kuwahara J, Kitano Y, Amano N, Umekage M, Kitaoka F, Tanaka A, Okada C, Takasu N, Ogawa S, Yamanaka S, Takahashi M (2017) Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med 376: 1038–1046.

Mangeot PE, Risson V, Fusil F, Marnef A, Laurent E, Blin J, Mournetas V, Massouridès E, Sohier TJM, Corbin A, Aubé F, Teixeira M, Pinset C, Schaeffer L, Legube G, Cosset FL, Verhoeyen E, Ohlmann T, Ricci EP (2019) Genome editing in primary cells and in vivo using viral-derived Nanoblades loaded with Cas9-sgRNA ribonucleoproteins. Nat Communications 10: 45.

Matsuda T, Irie T, Katsurabayashi S, Hayashi Y, Nagai T, Hamazaki N, Adefuin AMD, Miura F, Ito T, Kimura H, Shirahige K, Takeda T, Iwasaki K, Imamura T, Nakashima K (2019) Pioneer Factor NeuroD1 Rearranges Transcriptional and Epigenetic Profiles to Execute Microglia-Neuron Conversion. Neuron 101: 472–485.

Miller JD, Ganat YM, Kishinevsky S, Bowman RL, Liu B, Tu EY, Mandal PK, Vera E, Shim JW, Kriks S, Taldone T, Fusaki N, Tomishima MJ, Krainc D, Milner TA, Rossi DJ, Studer L (2013) Human iPSC-based modeling of late-onset disease *via* progerin-induced aging. Cell Stem Cell 13: 691–705.

Miyoshi N, Ishii H, Nagano H, Haraguchi N, Dewi DL, Kano Y, Nishikawa S, Tanemura M, Mimori K, Tanaka F, Saito T, Nishimura J, Takemasa I, Mizushima T, Ikeda M, Yamamoto H, Sekimoto M, Doki Y, Mori M (2011) Reprogramming of mouse and human cells to pluripotency using mature microRNAs. Cell Stem Cell 8: 633–638.

Morgani SM, Metzger JJ, Nichols J, Siggia ED, Hadjantonakis AK (2018) Micropattern differentiation of mouse pluripotent stem cells recapitulates embryo regionalized cell fate patterning. eLife 7: e32839.

Morizane A, Kikuchi T, Hayashi T, Mizuma H, Takara S, Doi H, Mawatari A, Glasser MF, Shiina T, Ishigaki H, Itoh Y, Okita K, Yamasaki E, Doi D, Onoe H, Ogasawara K, Yamanaka S, Takahashi J (2017) MHC matching improves engraftment of iPSC-derived neurons in non-human primates. Nat Comm 8: 385.

Nakagawa M, Taniguchi Y, Senda S, Takizawa N, Ichisaka T, Asano K, Morizane A, Doi D, Takahashi J, Nishizawa M, Yoshida Y, Toyoda T, Osafune K, Sekiguchi K, Yamanaka S (2014) A novel efficient feeder-free culture system for the derivation of human induced pluripotent stem cells. 4: 3594.

Nakano KK, Tyler HR (1971) A double-blind study of the effects of levodopa in Parkinson's disease. Neurology 21: 1069–1074.

Nguyen HN, Byers B, Cord B, Shcheglovitov A, Byrne J, Gujar P, Kee K, Schüle B, Dolmetsch RE, Langston W, Palmer TD, Pera RR (2011) LRRK2 Mutant iPSC-Derived DA neurons demonstrate increased susceptibility to oxidative stress. Cell Stem Cell 8: 267–280.

Nielsen MS, Glud AN, Møller A, Mogensen P, Bender D, Sørensen JC, Doudet D, Bjarkam CR (2016) Continuous MPTP intoxication in the göttingen minipig results in chronic parkinsonian deficits. Acta Neurobiol Exp 76: 199–211.

Nolbrant S, Heuer A, Parmar M, Kirkeby A (2017) Generation of high-purity human ventral midbrain dopaminergic progenitors for in vitro maturation and intracerebral transplantation. Nature Protocols 12: 1962–1979.

Okumura T, Horie Y, Lai CY, Lin HT, Shoda H, Natsumoto B, Fujio K, Kumaki E, Okano T, Ono S, Tanita K, Morio T, Kanegane H, Hasegawa H, Mizoguchi F, Kawahata K, Kohsaka H, Moritake H, Nunoi H, Waki H, Tamaru S-I, Sasako T, Yamauchi T, Kadowaki T, Tanaka H, Kitanaka S, Nishimura K, Ohtaka M, Nakanishi M, Otsu M (2019) Robust and highly efficient hiPSC generation from patient non-mobilized peripheral blood-derived CD34+ cells using the auto-erasable Sendai virus vector. Stem Cell Res Ther 10: 185.

Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 54: 403–414.

Paquet D, Kwart D, Chen A, Sproul A, Jacob S, Teo S, Olsen KM, Gregg A, Noggle S, Tessier-Lavigne M (2016) Efficient introduction of specific homozygous and heterozygous mutations using CRISPR/Cas9. Nature 533: 125–129.

Parmar M (2018) Towards stem cell based therapies for Parkinson's disease. Development 145: 156117.

Parmar M, Grealish S, Henchcliffe C (2020) The future of stem cell therapies for Parkinson disease. Nat Rev Neurosci 21: 103–115.

Pfeiffer HCV, Løkkegaard A, Zoetmulder M, Friberg L, Werdelin L (2014) Cognitive impairment in early-stage non-demented Parkinson's disease patients. Acta Neurol Scand 129: 307–318.

Pfisterer U, Kirkeby A, Torper O, Wood J, Nelander J, Dufour A, Björklund A, Lindvall O, Jakobsson J, Parmar M (2011) Direct conversion of human fibroblasts to dopaminergic neurons. Proc Natl Acad Sci 108: 10343.

Plummer S, Wallace S, Ball G, Lloyd R, Schiapparelli P, Quiñones-Hinojosa A, Hartung T, Pamies D (2019) A Human iPSC-derived 3D platform using primary brain cancer cells to study drug development and personalized medicine. Sci Rep 9: 1407.

Polo JM, Liu S, Figueroa ME, Kulalert W, Eminli S, Tan KY, Apostolou E, Stadtfeld M, Li Y, Shioda T, Natesan S, Wagers AJ, Melnick A, Evans T, Hochedlinger K (2010) Cell type of origin influences the molecular and functional properties of mouse induced pluripotent stem cells. Nat Biotechnol 28: 848–855.

Rane A, Rajagopalan S, Ahuja M, Thomas B, Chinta SJ, Andersen JK (2018) Hsp90 Co-chaperone p(23 contributes to dopaminergic mitochondrial stress *via* stabilization of PHD2: Implications for Parkinson's disease. NeuroToxicol 65: 166–173.

Recasens A, Dehay B, Bové J, Carballo-Carbajal I, Dovero S, Pérez-Villalba A, Fernagut PO, Blesa J, Parent A, Perier C, Fariñas I, Obeso JA, Bezard E, Vila M (2014) Lewy body extracts from Parkinson disease brains trigger α-synuclein pathology and neurodegeneration in mice and monkeys. Ann Neurol 75: 351–362.

Reinhardt P, Schmid B, Burbulla LF, Schondorf DC, Wagner L, Glatza M, Hoing S, Hargus G, Heck SA, Dhingra A, Wu G, Muller S, Brockmann K, Kluba T, Maisel M, Kruger R, Berg D, Tsytsyura Y, Thiel CS, Psathaki OE, Klingauf J, Kuhlmann T, Klewin M, Muller H, Gasser T, Scholer HR, Sterneckert J (2013) Genetic correction of a LRRK(2 mutation in human iPSCs links parkinsonian neurodegeneration to ERK-dependent changes in gene expression. Cell Stem Cell 12: 354–367.

Romero A, Parada E, González-Lafuente L, Farré-Alins V, Ramos E, Cacabelos R, Egea J (2017) Neuroprotective effects of E-PodoFavalin-15999 (Atremorine®). CNS Neurosci Ther 23: 450–452.

Ryan S D, Dolatabadi N, Chan S F, Zhang X, Akhtar MW, Parker J, Ambasudhan R, Lipton SA (2013) Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1α transcription. Cell 155: 1351–1364.

Saenger VM, Kahan J, Foltynie T, Friston K, Aziz TZ, Green AL, Van Hartevelt TJ, Cabral J, Stevner ABA, Fernandes HM, Mancini L, Thornton J, Yousry T, Limousin P, Zrinzo L, Hariz M, Marques P, Sousa N, Kringelbach ML, Deco G (2017) Uncovering the underlying mechanisms and whole-brain dynamics of deep brain stimulation for Parkinson's disease. Sci Rep 7: 9882.

Schaefer KA, Wu W-H, Colgan DF, Tsang SH, Bassuk AG, Mahajan VB (2017) Unexpected mutations after CRISPR-Cas9 editing in vivo. Nat Meth 14: 547–548.

Schapansky J, Khasnavis S, DeAndrade MP, Nardozzi JD, Falkson SR, Boyd JD, Sanderson JB, Bartels T, Melrose HL, LaVoie MJ (2018) Familial knockin mutation of LRRK2 causes lysosomal dysfunction and accumulation of endogenous insoluble α-synuclein in neurons. Neurobiol Disease 111: 26–35.

Scudamore O, Ciossek T (2018) Increased Oxidative Stress Exacerbates alpha-Synuclein Aggregation In Vivo. J Neuropathol Exp Neurol 77: 443–453.

Scudellari M (2016) How iPS cells changed the world. Nature 534: 310–312.

Seo J, Lee Y, Kim BS, Park J, Yang S, Yoon HJ, Yoo J, Park HS, Hong JJ, Koo BS, Baek SH, Jeon CY, Huh JW, Kim YH, Park SJ, Won J, Ahn YJ, Kim K, Jeong KJ, Kang P, Lee DS, Lim SM, Jin YB, Lee SR (2019) A non-human primate model for stable chronic Parkinson's disease induced by MPTP administration based on individual behavioral quantification. J Neurosci Meth 311: 277–287.

Shiba Y, Gomibuchi T, Seto T, Wada Y, Ichimura H, Tanaka Y, Ogasawara T, Okada K, Shiba N, Sakamoto K, Ido D, Shiina T, Ohkura M, Nakai J, Uno N, Kazuki Y, Oshimura M, Minami I, Ikeda U (2016) Allogeneic transplantation of iPS cell-derived cardiomyocytes regenerates primate hearts. Nature 538: 388–391.

Shirotani K, Matsuo K, Ohtsuki S, Masuda T, Asai M, Kutoku Y, Ohsawa Y, Sunada Y, Kondo T, Inoue H, Iwata N (2017) A simplified and sensitive method to identify Alzheimer's disease biomarker candidates using patient-derived induced pluripotent stem cells (iPSCs). J Biochem 162: 391–394.

Sidransky E, Lopez G (2012) The link between the GBA gene and parkinsonism. Lancet Neurol 11: 986–998.

Simón-Sánchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, Krüger R, Federoff M, Klein C, Goate A, Perlmutter J, Bonin M, Nalls MA, Illig T, Gieger C, Houlden H, Steffens M, Okun MS, Racette BA, Cookson MR, Foote KD, Fernandez HH, Traynor BJ, Schreiber S, Arepalli S, Zonozi R, Gwinn K, van der Brug M, Lopez G, Chanock SJ, Schatzkin A, Park Y, Hollenbeck A, Gao J, Huang X, Wood NW, Lorenz D, Deuschl G, Chen H, Riess O, Hardy JA, Singleton AB, Gasser T (2009) Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet 41: 1308–1312.

Soldner F, Laganière J, Cheng AW, Hockemeyer D, Gao Q, Alagappan R, Khurana V, Golbe LI, Myers RH, Lindquist S, Zhang L, Guschin D, Fong LK, Vu BJ, Meng X, Urnov FD, Rebar EJ, Gregory PD, Zhang HS, Jaenisch R (2011) Generation of isogenic pluripotent stem cells differing exclusively at two early onset Parkinson point mutations. Cell 146: 318–331.

Sommer A, Maxreiter F, Krach F, Fadler T, Grosch J, Maroni M, Graef D, Eberhardt E, Riemenschneider MJ, Yeo GW (2018) Th17 lymphocytes induce neuronal cell death in a human iPSC-based model of Parkinson's disease. Cell Stem Cell 23: 123–131.

Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) α-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci USA 95: 6469–6473.

Stanslowsky N, Haase A, Martin U, Naujock M, Leffler A, Dengler R, Wegner F (2014) Functional differentiation of midbrain neurons from human cord blood-derived induced pluripotent stem cells. Stem Cell Res Ther 5: 35.

Tagliafierro L, Zamora ME, Chiba-Falek O (2019) Multiplication of the SNCA locus exacerbates neuronal nuclear aging. Hum Mol Genet 28: 407–421.

Takahashi J (2019) Preparing for first human trial of induced pluripotent stem cell-derived cells for Parkinson's disease: an interview with Jun Takahashi. Regen Med 14: 93–95.

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131: 861–872.

Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663–676.

Tarnawski L, Eugster E, DeCamp L, Jovinge S (2019) The efficacy and safety of sendai viral reprograming of mouse primary cells using human vectors. Cell Reprogram 21: 78–88.

Tashiro K, Kawabata K, Inamura M, Takayama K, Furukawa N, Sakurai F, Katayama K, Hayakawa T, Furue MK, Mizuguchi H (2010) Adenovirus vector-mediated efficient transduction into human embryonic and induced pluripotent stem cells. Cell Reprogram 12: 501–507.

The Hd iPsc Consortium (2012) Induced pluripotent stem cells from patients with Huntington's disease show CAG-repeat-expansion-associated phenotypes. Cell Stem Cell 11: 264–278.

Thomas B, Mandir AS, West N, Liu Y, Andrabi SA, Stirling W, Dawson VL, Dawson TM, Lee MK (2011) Resistance to MPTP-neurotoxicity in α-synuclein knockout mice is complemented by human α-synuclein and associated with increased β-synuclein and Akt activation. PLoS One 6: e16706.

Trilck M, Hübner R, Frech MJ (2016) Generation and neuronal differentiation of patient-specific induced pluripotent stem cells derived from niemann-pick type C1 fibroblasts. Methods Mol Biol 1353: 233–259.

Van Kampen JM, Baranowski DB, Shaw CA, Kay DG (2014) Panax ginseng is neuroprotective in a novel progressive model of Parkinson's disease. Exp Gerontol 50: 95–105.

Van Kampen JM, Baranowski DC, Robertson HA, Shaw CA, Kay DG, Lewis P (2015) The progressive BSSG rat model of Parkinson's: Recapitulating multiple key features of the human disease. PLoS One 10: e0139694.

Vermilyea SC, Guthrie S, Meyer M, Smuga-Otto K, Braun K, Howden S, Thomson JA, Zhang SC, Emborg ME, Golos TG (2017) Induced pluripotent stem cell-derived dopaminergic neurons from adult common marmoset fibroblasts. Stem Cells Develop 26: 1225–1235.

Vierbuchen T, Ostermeier A, Pang ZP, Kokubu Y, Südhof TC, Wernig M (2010) Direct conversion of fibroblasts to functional neurons by defined factors. Nature 463: 1035–1041.

Vila M, Jackson-Lewis V, Vukosavic S, Djaldetti R, Liberatore G, Offen D, Korsmeyer SJ, Przedborski S (2001) Bax ablation prevents dopaminergic neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Proc Natl Acad Sci USA 98: 2837–2842.

Wakabayashi K, Hayashi S, Yoshimoto M, Kudo H, Takahashi H (2000) NACP/alpha-synuclein-positive filamentous inclusions in astrocytes and oligodendrocytes of Parkinson's disease brains. Acta Neuropathol 99: 14–20.

Wang S, Bates J, Li X, Schanz S, Chandler-Militello D, Levine C, Maherali N, Studer L, Hochedlinger K, Windrem M, Goldman SA (2013) Human iPSC-derived oligodendrocyte progenitor cells can myelinate and rescue a mouse model of congenital hypomyelination. Cell Stem Cell 12: 252–264.

Wang S, Zou C, Fu L, Wang B, An J, Song G, Wu J, Tang X, Li M, Zhang J, Yue F, Zheng C, Chan P, Zhang YA, Chen Z (2015) Autologous iPSC-derived dopamine neuron transplantation in a nonhuman primate Parkinson's disease model. Cell Discovery 1: 15012.

Wenning GK, Odin P, Morrish P, Rehncrona S, Widner H, Brundin P (1997) Short- and long-term survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease. Ann Neurol 42: 95–107.

Whone AL, Boca M, Luz M, Woolley M, Mooney L, Dharia S, Broadfoot J, Cronin D, Schroers C, Barua NU, Longpre L, Barclay CL, Boiko C, Johnson GA, Fibiger HC, Harrison R, Lewis O, Pritchard G, Howell M, Irving C, Johnson D, Kinch S, Marshall C, Lawrence AD, Blinder S, Sossi V, Stoessl AJ, Skinner P, Mohr E, Gill SS (2019) Extended treatment with glial cell line-derived neurotrophic factor in Parkinson's disease. J Parkinsons Dis 9: 301–313.

Wilson JMB, Khabazian I, Wong MC, Seyedalikhani A, Bains JS, Pasqualotto BA, Williams DE, Andersen RJ, Simpson RJ, Smith R, Craig UK, Kurland LT, Shaw CA (2002) Behavioral and neurological correlates of ALS-parkinsonism dementia complex in adult mice fed washed cycad flour. Neuro Molr Med 1: 207–221.

Windrem MS, Nunes MC, Rashbaum WK, Schwartz TH, Goodman RA, McKhann G 2nd, Roy NS, Goldman SA (2004) Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. Nat Med 10: 93–97.

Windrem MS, Schanz SJ, Guo M, Tian GF, Washco V, Stanwood N, Rasband M, Roy NS, Nedergaard M, Havton LA, Wang S, Goldman SA (2008) Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse. Cell Stem Cell 2: 553–565.

Yamashita T, Kawai H, Tian F, Ohta Y, Abe K (2011) Tumorigenic development of induced pluripotent stem cells in ischemic mouse brain. Cell Transplant 20: 883–891.

Yoo HS, Chung SJ, Chung SJ, Moon H, Oh JS, Kim JS, Hong JY, Ye BS, Sohn YH, Lee PH (2018) Presynaptic dopamine depletion determines the timing of levodopa-induced dyskinesia onset in Parkinson's disease. Eur J Nucl Med Mol I 45: 423–431.

Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA (2007) Induced pluripotent stem cell lines derived from human somatic cells. Science 318: 1917–1920.

Yusa K, Rashid ST, Strick-Marchand H, Varela I, Liu PQ, Paschon DE, Miranda E, Ordonez A, Hannan NR, Rouhani FJ, Darche S, Alexander G, Marciniak SJ, Fusaki N, Hasegawa M, Holmes MC, Di Santo JP, Lomas DA, Bradley A, Vallier L (2011) Targeted gene correction of alpha1-antitrypsin deficiency in induced pluripotent stem cells. Nature 478: 391–394.

Zhang S, Wang XJ, Tian LP, Pan J, Lu GQ, Zhang YJ, Ding JQ, Chen SD (2011) CD200-CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease. J Neuroinflammat 8: 154.

Zhao Y, Rafatian N, Feric NT, Cox BJ, Aschar-Sobbi R, Wang EY, Aggarwal P, Zhang B, Conant G, Ronaldson-Bouchard K, Pahnke A, Protze S, Lee JH, Davenport Huyer L, Jekic D, Wickeler A, Naguib HE, Keller GM, Vunjak-Novakovic G, Broeckel U, Backx PH, Radisic M (2019) A platform for generation of chamber-specific cardiac tissues and disease modeling. Cell 176: 913–927.

Zhou H, Martinez H, Sun B, Li A, Zimmer M, Katsanis N, Davis EE, Kurtzberg J, Lipnick S, Noggle S, Rao M, Chang S (2015) Rapid and efficient generation of transgene-free iPSC from a small volume of cryopreserved blood. Stem Cell Rev Rep 11: 652–665.

Zhu L, Sun C, Ren J, Wang G, Ma R, Sun L, Yang D, Gao S, Ning K, Wang Z, Chen X, Chen S, Zhu H, Gao Z, Xu J (2019) Stress-induced precocious aging in PD-patient iPSC-derived NSCs may underlie the pathophysiology of Parkinson's disease. Cell Death Disease 10: 105.