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Personalized Medicine Approach and the Application of iPSCs in Neurological Diseases

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Abstract:
A number of animal disease models have been created in the past to investigate the molecular basis of neurological diseases and identify novel treatments, but their effectiveness has been limited by the absence of comparable animal models. There are still several important problems that need to be overcome, including the high expenses associated with creating animal models, ethical issues, and a lack of similarity to human disease. More than 90% of medications fail in the last stage of the human clinical trial as a result of inadequate early screening and assessment of the molecules. A novel strategy based on induced pluripotent stem cells has been developed to get around these restrictions (iPSCs). A new road map for clinical translational research and regeneration treatment has been made possible by the discovery of iPSCs. In this paper, we investigate the potential use of patient-derived iPSCs to neurological disorders as well as their significance in scientific and clinical studies for the creation of disease models and a road map for the next of medicine. The role of human iPSCs in the most prevalent neurodegenerative illnesses (such as Parkinson's and Alzheimer's disease, diabetic neuropathy) was evaluated. The patient-on-a-chip idea, where iPSCs may be cultivated on 3D matrices within microfluidic devices to produce an in vitro disease model for tailored medication, is another new development in the field of personalized medicine that we looked into.

INTRODUCTION

The development of in vitro disease models for a variety of ailments, including neurodegenerative disease, diabetes mellitus, and heart, liver, lung, and kidney disease, was made possible by the discovery of induced pluripotent stem cells (iPSCs) technology in 2007 (1). It is crucial to develop a more suitable drug discovery strategy to close the gap between pre-clinical research and human clinical trials. Reprogramming differentiated cell types into pluripotent stem cells, such as patient fibroblasts or peripheral blood mononuclear cells (PBMCs), has been created and employed for drug testing, greatly enhancing the disease model system for in vitro drug research. This technology is being used to research neurological diseases such as ataxia, amyotrophic lateral sclerosis, multiple sclerosis, spinal cord injury and Parkinson's disease (2). Additionally, it makes it possible for researchers to study and comprehend how complex human tissues, including the brain and heart, respond to newly found medications. In this strategy, blood cells or biopsies are used to create and maintain patient-specific iPSC cell lines (3). The illness state is replicated in vitro in a petri dish using these iPSCs that have been reprogrammed into certain cell types of interest. Because of their propensity to proliferate and differentiate, human-iPSCs can be used to study the physiology of impacted cell types on tissue culture plates. This approach may also be used to test and find disease-specific medicines in a petri dish in vitro. These pre-clinical investigations in petri dishes offered the first proof of concept and a viable method for studying disease molecular mechanisms and screening promising compounds for medication development and cytotoxicity research (4).

Surprisingly, only medications that have been evaluated and pre-tested in pre-clinical research are being examined in human clinical trials. Due to the severe assessment requirements in pre-clinical research, these applicants should ideally work in human clinical trials. However, a significant disparity has been seen between human clinical trials and pre-clinical studies. For example, despite large financing prospects for clinical trials (up to USD 42.5 billion), the outcomes in Alzheimer's disease have been dismal, with a 95% failure rate. Furthermore, only six medications suggested for Alzheimer's disease (AD)

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were licensed by the US Food and Drug Administration (FDA) between 1995 and 2021 (5).

We examine the role of human iPSCs in scientific and clinical research in this review. We also look at recent iPSC-related breakthroughs in clinical research and examine the importance of iPSCs in cellular treatment, personalized medicine, and ongoing clinical trials for Parkinson's disease (PD) and Alzheimer's disease (AD).

What are iPSCs ?

Yamanaka, S., and Takahashi, K., made a significant discovery in the early 2000s when they successfully produced new types of stem cells, known as induced pluripotent stem cells, from mouse embryonic and adult fibroblast cultures (iPSCs)(6). OCT4, SOX2, KLF4, and C-MYC, collectively known as the Yamanaka factors, were added to the culture media in order to change how the fibroblasts' genome was expressed. The Yamanaka factors work with viral vectors, particularly retroviral and lentiviral transduction, to help induce and maintain the pluripotent state. iPSCs have been extensively employed for research on possible cell therapies, disease modeling, and pharmacological screening of neuroprotective substances (7).

Additionally, iPSCs with organoids and gene editing techniques like CRISPR-Cas9 transform these cells into a highly adaptable tool for regenerative medicine and drug screening to assess substances with the potential to treat a variety of diseases, leading to the identification of clinical candidates and the approval of some for their application. It's important to recognize their drawbacks, though, including their high cost, the length of time required for development, the requirement to downregulate the MHC (Mayor Histocompatibility Complex) in the host cells if the iPSCs-derived cells will be transplanted in order to limit immune recognition, the unique culture conditions, reprogramming and differentiation processes' contribution to karyotype abnormalities caused by genetic instability, which iPSCs suffer from (9, 10).

Non-integrating techniques, including as synthetic mRNAs, Sendai virus, and episomal DNAs, have been developed in recent years to address the problems caused by genomic instability and lower the hazards associated with vectors (11). Furthermore, genome editing methods offer the chance to incorporate genetic modifications into iPSCs in a site-specific way, creating isogenic iPSCs lines, which are crucial in sporadic and polygenic illnesses (11).

Although technically iPSCs may be produced from any tissue in the body, the most commonly used sources are fibroblasts and peripheral blood mononuclear cells due to their accessibility. The creation of iPSCs begins with the recovery of somatic cells from a patient or an animal model, which are then transduced with a virus comprising the reprogramming factors (12, 13). Once the reprogramming is complete, variations can be seen in the cultured cells, forming colonies that resemble ESCs. As a result, the cells are then gathered for more expansion for several passages to ensure the conservation of their distinctive morphology. To ensure their resemblance, these cells should express ESC antigens such SSEA-4 and TRA-1-80. Other procedures that might be carried out include chromosomal analysis to check for a normal karyotype or to find potential translocations (14).

The function of iPSCs in neurodegenerative disorders

Recent advancements in the capacity to convert patient somatic cells into inducible pluripotent stem cells (iPSCs) have enabled a fresh method of producing disease-relevant cells for in vitro disease modeling (15). Clinicians are in need of novel treatments for neurodegenerative illnesses. Despite sound clinical research, it has been accepted that the medication treatments that have been developed fall short of expectations. Human iPSCs can, in theory, differentiate into any cell type in the human body; thus, patient iPSCs can provide a source of cells with a specific constellation of genetic variants associated with pathogenesis in the appropriate microenvironment (15). As a result, iPSCs are frequently used in well-established human disease models, including both developmental and adult-onset diseases, as two-dimensional (2D) cell cultures or three-dimensional (3D) organoids. Prior to the development of iPSC technology and iPSC-based modeling systems, animal models, primary brain cells, and immortal cell lines all made significant contributions to our knowledge of neurological illnesses. However, all of these models have limits, which drives the urge to create a better modeling system (16). For animal models, species differences constitute a barrier to completely reproduce disease characteristics, resulting in a high failure rate

Table 1. Advantages and limitations of iPSCs technology (8)

Advantages	Limitations
ESC use-related ethical and religious concerns are eliminated.	Reprogramming's efficiency is often low.
Immune rejection is less likely.	Tumorigenesis
Donor cells are quickly and painlessly collected, and no embryos are destroyed.	Insertional mutagenesis risk associated with virus-based delivery methods
Accessible to many patients, as opposed to ESCs which are constrained by ethical consideration.	Increase chance of development of disease due to factors used.

in animal-model-based medication development. In the final stage of the human clinical trial, more than 90% of pre-clinically successful medicines are found to be ineffective (17, 18).

This indicates that human biology is frequently poorly predicted by animal models. Developing a degenerative disease model is a difficult task. Researchers have either altered the expression of a specific gene to create a cell culture model or created a knockout animal model. These models, however, might not be called a perfect illness model that reflects human pathophysiology. It is also extremely difficult to collect human brains postmortem for scientific research due to ethical concerns. Even if a human brain is available, brain tissues for study are extremely degradable and immunologically mature (19). Given its benefits over the previously described modeling methods, iPSC-based disease modeling is becoming increasingly popular for investigating neurological illnesses.Because iPSCs reprogrammed from human somatic cells are derived from humans, they eliminate the issues associated with employing animal models. iPSCs are easily grown and provide an infinite resource for further differentiation into cell types of interest (19). Above all, iPSCs derived from patient somatic cells preserve their original genomic characteristics, such as gene mutations and chromosomal abnormalities (19).

iPSCs in PD

The second most prevalent neurodegenerative condition is Parkinson's disease PD, which is characterized by stiffness, bradykinesia, postural instability, and static tremors. The brains of PD patients experience widespread neuronal loss, particularly due to the steadily deteriorating dopaminergic neurons in the substantia nigra compacta (20, 21). The central and peripheral nervous systems' remaining neurons have inclusion bodies (Lewis bodies) containing -synuclein. Synuclein alpha (SNCA), leucine-rich repeat kinase 2 (LRRK2), PTEN-induced putative kinase 1 (PINK1), parkin RBR E3 ubiquitin protein ligase (PARK2), and cytoplasmic protein sorting (VPS35) are examples of common PD-related mutant genes (21, 22). Additionally linked to PD is the CHCHD2 mutation. The study of PD molecular mechanism has considerably benefited from the development of induced pluripotent stem cells. From PD patients, a successful human iPSC line was created. In order to create iPSCs, Wang et al. (2018) transfected dermal fibroblasts from 52-year-old PD patients with episomal plasmids expressing OCT3/4, SOX2, KLF4, LIN28, and L-MYC. A CHCHD2 mutation is present in the produced iPSCs line (ZZUi007-A) (23). An iPSCs line (201B7) was created by Takahashi et al. in 2007 using the dermal fibroblasts of a healthy donor. At Kyoto University, fibroblasts were reprogrammed utilizing retroviral transduction to express OCT4, SOX2, KLF4, and MYC. They function as a "normal" check (24).

A human iPSCs line (B7PA21) was produced from PD patients with PARK2 mutations by Suda et al. in 2018. Ghrelin receptor expression was shown to be down-regulated in PD-iPSC-derived dopaminergic neurons compared to healthy controls. Additionally, creating the PARK2-KIKO line from 201B7 using CRISPR-Cas9 technology also mirrored the PARK2 gene's lack of function (25). Phospho-ubiquitin signaling was shown to be impacted in human dopaminergic neurons with Parkin or PINK1 mutations by Shiba-Fukushima et al. in 2017. Additionally, it was discovered that human dopaminergic neurons with Parkin or PINK1 mutations have poor control of axonal mitochondrial transport and phospho-ubiquitin signaling (25). Schweitzer et al 2020.'s study demonstrated the autologous transplantation of iPSC dopaminergic progenitor cells into the midbrain of PD patients. Clinical grade iPSCs were created in vitro, evaluated for immunogenicity using a humanized mouse model, and then transplanted into the putamen of PD patients without the need of immunosuppressive drugs. Fluorine-18-L-dihydroxyphenylalanine was used in positron emission tomography to predict graft survival (26). By reprograming OCT3/4, SOX2, c-MYC, KLF4, and BCL-XL, Chen et al., 2021 showed that an iPSCs line could be created from PBMCs of a 32-year-old PD patient with homozygous mutation of c.189dupA in PARK7 (FJMUUHi001). The generated iPSCs were able to display pluripotency markers and differentiate into three germ layers (27).

iPSCs in AD

A neurological, life-limiting, and deadly condition known as dementia causes gradual cognitive decline, behavioral issues, and loss of everyday functioning. The most frequent cause of dementia, accounting for 50% to 70% of dementia cases globally, is Alzheimer's disease (AD) (28). There are 50 million individuals living with dementia globally, according to the 2018 World Alzheimer's Disease Report. An additional incidence of AD is reported every three seconds worldwide, and by 2050, there will likely be 152 million cases (29). It is believed that iPSCs can develop into many different types of cells, including neurons and neurospheres. iPSCs may be utilized to create and automate neuronal subtypes, as demonstrated by experiments done both in vitro and after transplanting cells into the mouse brain (30). For instance, it is possible to analyze the inflammatory response of AD using glial cells produced from iPSCs. iPSCs were employed in another investigation with a mouse model of AD to produce macrophages that could express the A-degrading protease neprilysin (31, 32).

Michael Peitz et al. (2018) showed that using Sendai

virus vectors that encode for the transcription factors OCT4, SOX2, KLF4, and c-MYC, peripheral blood cells from a male AD patient may be transformed into a human iPSCs line. In addition to expressing differentiation into all three germ layers and maintaining the APOE"4/"4 genotype, a significant risk factor for sporadic late-onset AD, the described iPSCs line (33). The iPSCs were created by Liu et al., 2020 from individuals with sporadic Alzheimer's disease (sAD). The Sendai virus, which expresses Oct3/4, Sox2, c-Myc, and Klf4 transcription factors, was used to reprogramme PBMCs (34). An 87-year-old female donor with the APOE3 ("3/"3) alleles' peripheral blood mononuclear cells were used to create iPSCs by Zhang et al. in 2021. The ability of iPSCs to produce pluripotency markers such NANOG, OCT4, and SSEA4 coupled with a normal karyotype was greater than 97% (35). One of the most useful resources for understanding sAD pathogenesis in vitro is the created iPSCs line. Arber et al. demonstrated that iPSCs provide a useful model for examining possible cell dysfunction brought on by genetic fAD mutations by simulating APP processing and A synthesis in the setting of fAD-APP and PSEN1 mutations (36). However, there are significant barriers to the therapeutic usage of iPSCs due to the following unanswered questions: Teratoma development, long-term effectiveness and safety, tumorigenicity, immunogenicity, patient genetic abnormalities, ideal reprogramming, and other factors (37).

iPSCs in diabetic neuropathy

A major cause of death globally, diabetic mellitus (DM) is regarded as a chronic, systemic metabolic disorder. The World Health Organization estimates that there will be 693 million people worldwide with diabetes in 2045, up from just 451 million in 2017 (37). One of the severe microvascular consequences of diabetes mellitus (DM), diabetic nephropathy (DN), is a major risk factor for renal failure in individuals with end-stage renal disease. Although hyperglycemia is a significant risk factor for developing DN, other traits, including glycation end products and the overexpression of certain growth factors, are also connected to its etiology [38]. Additionally, excessive amounts of reactive oxygen might cause the kidney to produce inflammatory cytokines, which quickens the development of DN (38). Unfortunately, there are currently no medications that can stop DN from progressing. The present treatment options are restricted to RAAS blockage, rigorous management of hyperglycemia and blood pressure (39).

DN is linked to negative alterations in the peripheral nervous system, such as myelin degradation and a reduction in nerve conduction velocity (40). The myelin sheath is a multilayered membrane created in the peripheral nervous system by the development of Schwann cells' plasmatic membrane. When peripheral axons are working properly, Schwann cells are crucial because they protect and support both myelinated and non-myelinated peripheral nerve fibers (41). This support consists of both chemical and physical processes, and the release of various neurotrophic chemicals by Schwann cells. Based on this knowledge, many research teams examined the impact of applying Schwann cells to animal models with peripheral neuropathy (41).

Himeno et al. showed that certain mesenchymal stem cells (MSC)-like cells produced from iPSCs engraft to the peripheral nerve and express S100, a Schwann cell marker, when implanted to diabetic mice's thighs. This finding suggests that transplanted cells can actually create peripheral nerve tissue. Additionally, blood flow and capillary density in the soleus muscle of diabetic mice improved after transplantation of MSC-like cells. Therapy with MCS-like cells improved diabetic physiological deficits from a functional standpoint, highlighting the positive impact of such treatment on diabetic peripheral neuropathy (42).

iPSCs have effectively been differentiated into kidney cells in several studies, which may have an impact on how DN is treated. The iPSCs' ability to develop into kidney cells with podocyte features was initially described by Bi et al. iPSCs podocytes enhanced the mRNA expression and protein localization of podocyte markers such synaptopodin, renin, and WT-1 after 10 days of focused differentiation while downregulating the stem cell marker OCT3/4 (43). Human ES cells and iPSCs (referred to collectively as hPSCs) were shown to stably and quickly differentiate into pluripotent cells by chemical induction of the efficient small molecule inhibitor CHIR99021 (CHIR) of GSK-3, which can replicate the formation of mesoderm in developing embryos followed by fibroblast growth factor-2 (FGF-2) and RA and then form tubular structures upon growth factor w. Lam, A. Q. et al (43).

Experimental investigations have shown that MSCs can be employed to treat DN. However, the precise causes of DN have not been fully understood, and the molecular mechanisms for MSC-based DN treatment are currently being researched (44). MSCs' plasticity in regenerative applications was first celebrated since they are multipotent cells with the ectopic capability of homing and differentiating into numerous cell types in response to particular stimuli, including glomerular endothelial cells (44). As far as we are aware, there hasn't been a clinical trial employing iPSCs as a treatment for diabetic neuropathy patients. But there is a fascinating research that employed iPSCs from a patient with idiopathic small fiber neuropathy to identify the best course of action for that patient. The utility of iPSCs in drug development and testing in

general, as well as in customized medicine to find the best cure for diabetic neuropathy or other disorders, is shown by this example.

iPSCs' and personalized medicine

It has been shown that iPSCs play a crucial role in cellular therapy, which might lead to human clinical trials and offer a treatment roadmap in the future (45). Patient-derived iPSCs can also serve as a special model for comprehending how diseases arise. Additionally, it can aid in drug testing and offer fresh perspectives for creating "new future medicines." A brand-new area of personalized medicine based on cellular treatment has emerged: regeneration therapy. A particular drug is created for a patient through personalized medicine using their pharmacogenomic and pharmacogenetic data (45).

The idea of using iPSCs to simulate a disease in vitro is based on their exceptional ability to perpetually divide themselves and their propensity to give birth to every type of cell in the human body (46). iPSCs might therefore offer an infinite pool of cell types that would otherwise not be able to get, such as the motor and dopaminergic neurons afflicted in ALS and PD. The primary benefit of iPSC technology is that it makes it possible to create pluripotent cells from any person in the context of that person's unique genetic identity, including people with sporadic disease and those suffering from complex multifactorial diseases with unknown genetic identities, like autism spectrum disorders (47). A number of recent studies have documented the effective creation of patient-specific iPSC lines from patients suffering from a variety of disorders. However, in a few cases, effective disease modeling has been established. Ebert et al., for example, reported the development of iPSC-derived motor neurons from a patient with a hereditary type of spinal muscular atrophy (SMA), a neurodegenerative illness characterized by the loss of lower motor neurons (48).

Because everyone reacts differently to different types of diseases, it is critical to study personalized medicine or personalized pharmacology. It might be caused by a combination of variables such as genetics, epigenetics, environment, or demographics such as age, gender, and ethnicity (49). These factors, when combined, can accelerate the progression of any disease. However, some authors contend that genetic factors are the most important risk factors in complex diseases, such as neurological disorders. Furthermore, the interaction of genetic, environmental, demographic, and lifestyle factors is critical in disease development (50).

The development of iPSCs technology in 2007 changed the area of personalized medicine by enabling various methods of drug screening; it is also a suitable candidate for tailored cell treatments. The compound attrition rate has a significant impact on drug development costs. Preclinical testing of 5,000-10,000 compounds has been conducted for each medicine that enters the market. More accurate predicted toxicity models would assist in lowering these expenditures (47, 51).

iPSCs also provide interesting potential for high throughput drug screening of particular disease characteristics. This remarkable capacity in toxicity investigations has the potential to improve the efficiency of innovative human medication development while lowering drug attrition in the last phases of development and hence costs (52). The accurate prediction of human drug toxicity is a critical step in the drug development process. Hepatotoxicity and cardiotoxicity, in particular, are two main reasons of medication failure during preclinical testing, while individual response variability to prospective therapeutic agents is also a big issue in effective drug development (52). The benefit of iPSC technology is that it allows for the creation of a library of cell lines that may reflect the genetic and maybe epigenetic diversity of a wide range of populations. Because iPSCs may develop in culture continuously, they might supply an infinite source of any required specialized cells. The ultimate objective of this technique is to employ an in vitro disease model to develop innovative medications to treat the condition (53).

Organs-on-a-chip based on iPSCs for drug screening

In vitro models, such as "organon-a-chip" (OoC) technology, have advanced as a new avenue in scientific research. OoC technology is a revolutionary approach to testing drugs for human clinical trials (54). A potential technique is iPSC-based OoC, which blends iPSC-derived 2D and 3D cell cultures with microfluidic devices. iPSC can develop as a monolayer in 2D or embedded in 3D matrices within the OoC. Major changes in proliferation, migration, differentiation, drug toxicity resistance, and gene expression were discovered when 2D and 3D cell cultures were compared (55). A microfluidic system gives mechanical and chemical physiological stimuli (e.g., compression and chemical gradients) and perfusion to the hosted cells, assuring a dynamic environment more akin to the in vivo situation. The "3Rs paradigm" (Minimize, Substitute, Refine for in vivo animal testing), for which these in vitro models have already been utilized forecast drug absorption, distribution, metabolism, and excretion and identify potential drug-induced toxicities, may be aided by the iPSCs-based OoC technology (55).

Reprogrammed iPSCs obtained from patients with diverse genetic origins can also be used to evaluate the safety and efficacy of medications in personalized medicine, where iPSCs can be cultivated on 3D matrices

within microfluidic devices utilizing techniques such as micromachining, 3D printing, and hydrogels. These circumstances reflect a novel technique that is more similar to in vivo situations (56).

An oral medication is absorbed by the gut, processed by the liver, transported to the target organs via blood flow, and eliminated by the kidneys (57). As a result, the main OoC presently being developed include the gut for absorption (58), the liver for metabolism, the kidney for elimination (59), the heart (60), the lung, the blood-brain barrier (BBB) (61), and the brain. To mimic how drugs are transported from the bloodstream to tissues and then to the target organ, the OoC must be vascularized through an endothelium. As a result, several research teams have enhanced their microfluidic apparatus for the particular purpose of drug discovery and screening by include an endothelium.

Patients' iPSC-derived intestinal organoids micro-engineered chips, which simulate inflammatory bowel illness, were utilized to examine medication absorption (62). The most prevalent reason of medication failure is hepatotoxicity caused by the medicine. Recently, drug metabolism, detoxification, and hepatotoxicity were studied on a chip using iPSC-derived hepatocytes or iPSC-derived liver organoids. Terfenadine, Tolcapone, Trovafloxacin, Troglitazone, Rosiglitazone, Pioglitazone, Lipopolysaccharide (LPS), and Caffeine, for example, were tested on a microfluidic platform equipped with a four-cell liver acinus microphysiology system comprised of PHH or iPSC-HEPs and three different human cell lines for NPCs (63).

The integration of these OoC with human iPSCs may pave the way for a new generation of OoC (dubbed patient-on-a-chip) that will permit the study of drug responses in a specific user. Fanizza et al., 2022 discussed and expanded on the role of iPSCs in drug screening for personalized medicine, particularly for neurodegenerative diseases. The translational value of OoC was investigated in order to develop more realistic disease models (64). The value of OoC has been greatly increased by the use of patient-specific iPSCs in the development of a new generation device known as "patient-on-a-chip." Furthermore, multi-OoC devices may allow crosstalk between different types of cells that replicate a genuine physiological environment extremely similar to in vivo circumstances and may be valuable in studying medication pharmacodynamics and pharmacokinetics in personalized medicine (65).

3D models of neurodegenerative diseases based on iPSCs

Brain organoids provide a new frontier in the modeling of neurodegenerative disorders. Organoids are complicated three-dimensional in vitro structures derived from pluripotent stem cells capable of self-organization and self-renewal. Organoids produced from patient-iPSCs have been utilized to examine a variety of illnesses (66). These models successfully reproduce the illnesses' main pathological markers, and several of them have been employed for drug screening studies in AD/PD (67). Shortly, the γ-secretase inhibitor DAPT, as well as heparin and heparinase, lower Aβ levels in AD-iPSC-derived cortical organoids. Compound E (Comp-E) with a BACE-1 γ-secretase inhibitor (γ-secretase inhibitor IV) decreased amyloidosis and Tau pathology in an organoid model of Alzheimer's disease (68). An organoid model of sporadic PD revealed increased caspase-3 cleavage in DA neurons in response to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahy-dropyridine (MPTP), whereas administration of the LRKK2 inhibitor GSK2,578,215A resulted in a decrease in phosphorylated-synuclein levels and improved DA neuron survival (69).

There are other non-organoid-based iPSC-based 3D static models, such as a hydrogel-based AD model that permits the investigation of early phases of Aβ oligomerization, or an AD iPSC-derived scaffold-free spheroid with a proteome profile equivalent to post-mortem AD brains (70). Rouleau et al. used an intriguing approach, developing an AD patient-derived iPSC-based 3D culture of neurons and glial cells that was stably maintained for over 2 years. Importantly, this cell culture had elevated levels of pathogenic -amyloid, Tau, and oxidative stress indicators (71). Overall, our findings show that 3D models are a powerful tool for simulating the key aspects of neurodegenerative disorders such as Alzheimer's and Parkinson's. However, 3D models have significant disadvantages, including limited repeatability and a lack of vascularization, which is required to imitate inflammation or medication distribution, both of which are important aspects in neurodegenerative diseases (72).

Conclusion and future perspectives

The current advancement in iPSC technology has created a whole new path for clinical research. However, physicians and researchers are concerned about obstacles like as irreproducibility, epigenetic changes, genetic instability, high cost, and delay. There has been considerable progress toward practical use of reprogramming methods since the first description of iPSC production. However, iPSC-based treatments are still in their infancy, with numerous obstacles to overcome before clinical applications can be realized. Individual iPSC derivation techniques have yet to be widely shown for producing cell populations for cell replacement treatment, disease modeling, and drug development, and research assessing the equivalency of different kinds of iPSCs are highly awaited. Furthermore, thorough characterization of the functioning of iPSC-derived somatic cells, as well as

their functional equivalency with in vivo counterparts, is required. The capacity to create disease-relevant somatic cells limits the application of the benefits that iPSCs provide, and considerable obstacles remain in establishing pathways that quickly lead to pure and functional populations of numerous disease-relevant cells. Given the tremendous speed of progress in the iPSC area, the capacity to take a patient's own cells, fix the disease allele, and then return those cells to the patient in a genetically and physiologically right condition is likely to be the future of customized stem cell treatment.

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