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Review

Overview of Representative Clinical Trials Using Human Pluripotent Stem Cell-Differentiated Cells

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Abstract: Human pluripotent stem cells (hPSCs) can be differentiated into any type of tissue cells in the human body. Several clinical trials have been started for the medical care of patients with organ failure, such as those with retinal degeneration diseases (including age-related macular degeneration), Parkinson's disease, type 1 diabetes, spinal cord injury, epilepsy, myocardial infarction, graft-versus-host disease (GvHD), and cancer, using specific hPSC-derived tissue cells such as retinal pigment epithelium cells, insulin-secreting progenitor cells, dopamine-secreting progenitor cells, oligodendrocytes, GABAergic neurons, cardiomyocytes, mesenchymal stem cells, and engineered natural killer cells. We discuss which cell sources or cell types are promising for clinical applications, such as (i) universal hPSCs or conventional hPSCs and (ii) mature differentiated cells or progenitor cells. Especially, we discuss the progress of clinical trials using hPSC-differentiated cells in this review.

Keywords: induced pluripotent stem cell-derived cells; embryonic stem cell-derived cells; clinical trial; age-related macular degeneration; progenitor cells

1. Introduction

The establishment of human embryonic stem cells (hESCs) by Prof. Thompson [1] followed by the establishment of human induced pluripotent stem cells (hiPSCs) by Prof. Yamanaka [2] has paved the way for stem cell therapy with cells originating from human pluripotent stem cells (hPSCs), which offer an unlimited cell source; hPSCs (hESCs and hiPSCs) can be differentiated into any specific tissue cells for the treatment of patients with damaged tissues and organs. The difference between hPSCs and adult stem cells such as dental pulp stem cells (DSCs), muse cells (one of mesenchymal stem cells, MSCs), bone marrow stem cells (BSCs), and adipose derived stem cells (ASCs) is that hPSCs do not have aging problems, whereas adult and fetal stem cells have limitation of proliferation, typically around 10–15 passage proliferation is the limitation of adult and fetal stem cell proliferation.

Several clinical trials have examined the transplantation of hPSC-derived cells into patients with damaged organs or tissues [3–28]. Some overviews of clinical trials using specific hPSC-differentiated cells have been published from the viewpoints of different professional disciplines [29–45]. Table 1 shows some landmark clinical trials utilizing hPSC-derived cells. The number of current clinical trials using hESC- and hiPSC-derived specific tissue or organ cells are summarized in Table 2. The first clinical trials of hPSC-derived cells studied the treatment of spinal cord injuries by transplantation of oligodendrocyte progenitor cells differentiated from hESCs (GRN-OPC1); these studies took place in 2010 as part of the Geron trial [46,47]. Unfortunately, the Geron trial was closed because of financial problems. GRN-OPC1 was renamed AST-OPC1 and was also used for clinical trials by Asterias Biotherapeutics in 2015 [48]. Unfortunately, transplantation of oligodendrocytes derived from hPSCs has not yet been reported except from the above trials. This is likely be because transplantation into the spinal cord

might damage the patient's spinal cord as the cells are injected through a needle. Furthermore, oligodendrocytes derived from hPSCs need to be transplanted soon (typically less than 1–2 weeks) after the spinal cord injury for the treatment to be effective [49,50]. These factors make it difficult for patients to decide whether they would like to receive a transplant of hPSC-derived oligodendrocytes despite the risk of spinal cord damage by the needle.

We will discuss some landmark clinical trials using hPSC-derived cells in the following sections.

Table 1. Timeline of landmark clinical trials utilizing hPSC-derived cells [a].

Year	Landmark Clinical Trials Using hPSC-Derived Cells	Disease Treated	Clinical Trial Number (Refs)
1998	(hESC generation by Thompson)	(Cell source)	
2007	(hiPSC generation by Yamanaka)	(Cell source)	
2010	Transplantation of hESC-derived oligodendrocyte progenitor cells	Spinal cord injury	NCT02302157 [46,47]
2011	Transplantation of hESC-derived RPE cells by Schawartz	AMD, SMD	NCT01345006, NCT01344993 [51,52]
2013	Transplantation of finrin gel patches containing hESC-derived cardiomyocytes	Heart failure	NCT02057900 [23,53]
2013	Transplantation of hiPSC-derived cell sheet	AMD	UMIN000011929
2014	Transplantation of hiPSC-derived pancreatic endoderm cells	Type 1 Diabetes	NCT02239354
2015	Transplantation of hESC-derived dopaminergic progenitors	Parkinson's disease	NCT03119636
2016	Transplantation of hiPSC-derived dopaminergic progenitors	Parkinson's disease	NCT02452723
2017	Transplantation of hiPSC-derived MSC	GvHD, Diabetic foot ulcer	NCT02923375 [54]
2018	Transplantation of hiPSC-derived astrocyte	Amyotrophic lateral sclerosis (ALS)	NCT03482050
2018	Transplantation of hiPSC-derived hepatocyte	Liver failure	JMA-IIA00412, ChiCTR2100052988
2019	Transplantation of hiPSC-derived cardiomyocyte sheet	Heart failure	NCT04696328
2019	Transplantation of hiPSC-derived NK cells	Cancer	NCT03841110
2020	Transplantation of hiPSC-derived retinal organoid sheet	Retinal Pigmenthasa	jRCTa050200027 [55]
2020	Transplantation of hiPSC-derived neural stem cells	Spinal cord injury	jRCTa031190228, UMIN000035074
2021	Transplantation of hESC-derived neural stem cells	Stroke	NCT04631406
2021	Transplantation of hiPSC-derived T cells	Cancer	NCT04629729
2022	Transplantation of hiPSC-derived cardiomyocytes	Heart failure	NCT04945018
2022	Transplantation of hESC-derived inhibitory GABAergic interneurons	Epilepsy	NCT05135091
2023	Transplantation of hiPSC-derived pancreatic cell	Type 1 Diabetes	NCT04786262
2024	Transplantation of hiPSC-derived dopamine secreting neuron	Parkinson's disease	NCT06145711, NCT06687837, NCT06422208

[a] RPE; retinal pigment epithelium, AMD; age-related macular degeneration, MSC; mesenchymal stem cell, NK cell; natural killer cell, SMD; Stargardt's macular dystrophy.

Table 2. The numbers of current clinical studies using specific hESC- and hiPSC-derived tissue or organ cells (until 1 May 2025).

hPSC Differentiated Cells	No. of Clinical Trials Using hPSC-Differentiated Cells	
	hESC-Differentiated Cells	hiPSC-Differentiated Cells
RPE cells	24	11
Retinal photoreceptor organoids	0	2
Corneal epithelium cells	0	1
Oligodendrocytes	3	0
Astrocytes	1	0
Neural stem cells	3	3
Dopamin secreting progenitors and neurons	9	11
Interneurons	2	0
MSCs	6	8
Cardiac cells, cardiac progenitor cells	2	10
Muscle stem cells	0	2
Chondrocytes	0	1
NK cells	1	20
T cells	0	3
Dendritic cells	1	0
Platelets	0	2
Hematopoietic stem cells	0	1
Pancreatic cells	7	0
Hepatocytes	1	0

2. History of Transplantation of hPSC-Derived Cells in Regenerative Medicine

2.1. Transplantation of hPSC-Derived RPE Cells for Medical Care of Retinal Digeneration Starting in 2011

In 2011, the second clinical trials in which hPSC-derived cells were transplanted were performed by Schwartz et al. to cure dry age-related macular degeneration (AMD) using hESC (H9)-derived retinal pigment epithelium (RPE) cells [51,52]. Dysfunction and loss of RPE cells are hallmarks of AMD (Figure 1) [56–58]). This is because the overlying photoreceptors start to degenerate without healthy RPE cell layers, whose functions are (a) phagocytosis of old and dead photoreceptor outer segments, (b) transportation of nutrients, and (c) re-isomerization of all-trans-retinal into 11-cis-retinal [59,60].

After Schwartz's clinical trials [51,52], many research groups started the subretinal transplantation of hPSC-derived RPE cells to cure dry and wet AMD and Stargardt disease (Stargardt's macular dystrophy, SMD) [6,11,12,14,61,62]; only one cell line of allogeneic hPSC-derived RPE cells was typically used for any patients, along with administration of mild or low-dose immunosuppressive medicine. This is because the eye and brain are weakly immunogenic [63–69]. Therefore, it is acceptable to transplant only one cell line of hPSC-derived cells into any patient for the treatment of damaged tissue or organ, although the patient needs to use immunosuppressive medicine for some period. One of the difficulties of treating AMD patients with hPSC-derived cells is that the transplantation site of hPSC-derived RPE cells is subretinal, which makes the procedure a technical challenge. At least, it is unrealistic to transplant hPSC-derived RPE cells into patient eyes subretinally once a week or even once a month. Currently, there are 24 clinical trials focusing on the transplantation of allogeneic hESC-derived RPE and 11 clinical trials using hiPSC-derived RPE cells, which are mostly allogeneic cells. Transplantation of hPSC-derived RPE cells is currently the most popular topic of clinical trials using hPSC-derived cells (Table 2).

Recently, hiPSC-derived corneal epithelium cells were transplanted into the eyes of patients with a limbal stem cell deficiency. Patients' disease stage and corrected distance visual acuity were reported to be improved in the treated eyes [70].

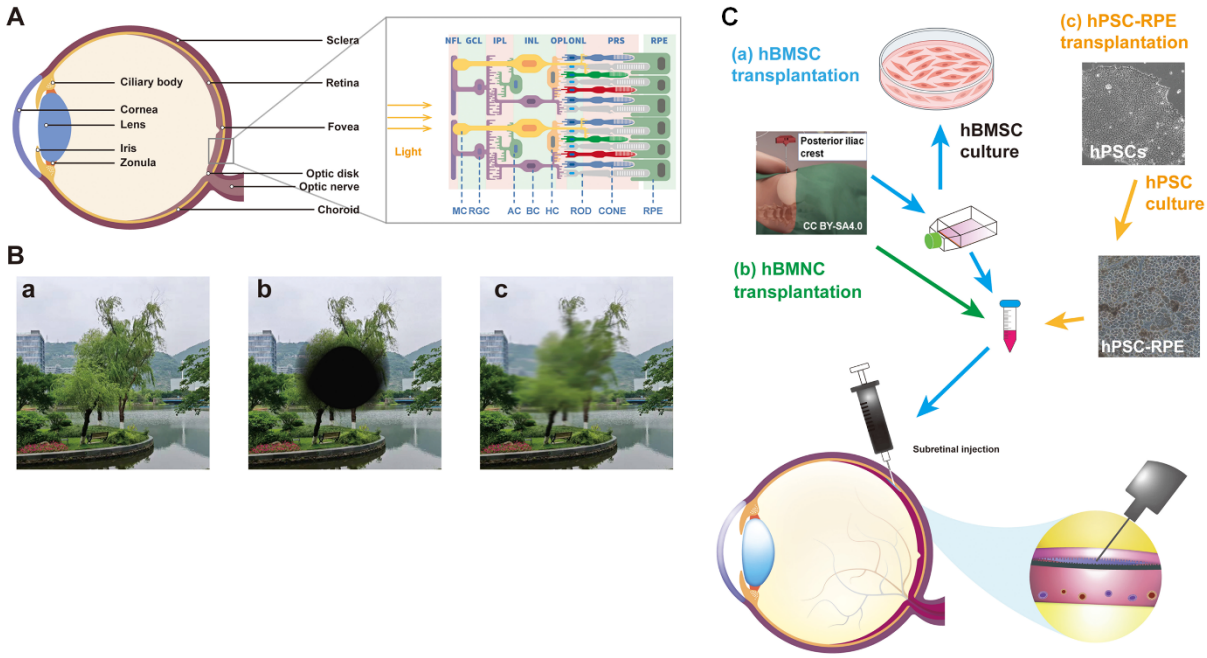

Figure 1. Eye configuration and age-related macular degeneration (AMD). (**A**) Eye configuration. (**B**) Images simulating the vision of a patient with late-stage AMD (**b**,**c**) and a person with normal vision (**a**). (**C**) Illustration of stem cell therapies for retinal macular degeneration disease.

2.2. Transplantation of hPSC-Derived Cardiac Cells for Medical Care of Myocardial Infarction Starting in 2013

A myocardial infarction (MI), typically known as a heart attack, generates when blood flow is reduced or stopped in one of the coronary arteries on the hearts, leading to infarction (tissue death) of the heart muscle. During MI, patients lose one billion or more cardiomyocytes, which are replaced by noncontractile scar tissue. Therefore, several groups started the transplantation of hPSC-derived cardiomyocytes or cardiac progenitor cells with 5–800 million cells for the treatment of MI, in which several cell formulations, such as cell suspensions (NCT04982081,

NCT05223894, etc.), spheroids (NCT049415018) and cell patches (NCT02057900, NCT04696328, and NCT04396899), were used [29,71–73].

In 2013, fibrin gel patches with entrapped hESC-derived cardiac progenitors were transplanted into the cardiac infarction area of six patients (NCT02057900). One year after treatment, no adverse issues caused by cell transplantation were reported, and some modest improvements in heart function were observed, although the number of clinical trials was too small to reach a definitive conclusion [23,53]. Following this clinical trial, several teams started clinical trials to transplant hPSC-derived cardiomyocytes into MI patients [18,19,21,53,74–80]. Several factors contribute to the function of hPSC-derived cardiomyocytes, such as cardiac maturation, purity, morphology of the products (sheet, scaffold, patch, suspension, and spheroid), cryopreservation or non-cryopreservation, and transplantation methods, which are the same as those used for other hPSC-derived cells. The functional fusion of transplanted hPSC-derived cardiomyocytes into patient hearts and the avoidance of side effects such as arrhythmias are important for future cardiac transplantation of hPSC-derived cells [29,53,74,75].

2.3. Transplantation of hPSC-Derived Pancreatic Endoderm Progenitor Cells for Medical Care of Type 1 Diabetes Starting in 2014

The transplantation of pancreatic endoderm progenitor cells (PEC-01) derived from hESCs into patients with type 1 diabetes was started by the company Viacyte in 2014 (NCT02239354) [29]. PEC-01 cells were entrapped in packages 3 x 8 cm in size (Encaptra) that could restrict the migration of immune cells into the site. PEC-01 cells could be obtained from hESCs in 12 days [81]. One of the merits of using progenitor cells from specific tissues or organs is that the preparation period is much shorter than that of mature cells. For example, a time frame of 27–43 days or more is necessary to prepare pancreatic beta cells (mature beta cells), which respond to glucose concentrations to regulate their insulin secretion [82,83]. A short differentiation period leads to reduced contamination of the final product of the cells, reducing the use of expensive bioactive molecules, including signaling molecules, proteins, inhibitors and agonists, and facilitating mass production of the cells for clinical transplantation. Typically, tissue or organ progenitor cells differentiate into mature cells in vivo [84,85].

The device entrapped with PEC-01 cells was subcutaneously transplanted, and the packages were removed from the patients after no secretion of insulins from the device. However, the cell survival in this device was not as good, probably because of the hypoxic conditions that the cells faced inside the device [86]. Therefore, in 2017, the device was modified to allow blood tube formation inside the device with small pores, which were made of nonwoven fabrics, where patients need to use immunosuppressive medicine. However, the device was invaded by patient-derived fibrosis, as approximately 25–40% of the PEC-01 cells remained in the device at 1–2 years after transplantation. Modest enhancement of C-peptide (a 31-amino-acid polypeptide) secretion was reported for 35% of patients [27], where C-peptide production is an index of transplanted pancreatic β cells, which are generated during the process of insulin biosynthesis within pancreatic β cells [87].

In 2019, a non-entrapped, hESC-derived mature pancreatic islet cell solution (VX-880, NCT04786262) was transplanted through the portal vein to patients receiving a chronic immunosuppression regimen. Twelve patients were transplanted with hESC-derived mature pancreatic islet cell solution (VX-880) one time, and all the patients displayed evidence of engraftment of mature pancreatic islet cells. All of the patients except one patient could reduce or be unnecessary for insulin injection [29]. Three patients reported insulin independence and excellent glycemic control with less severe hypoglycemic problems after one year of follow-up evaluation [29].

2.4. Transplantation of hPSC-Derived Dopaminergic Neurons for Medical Care of Parkinson's Disease Starting in 2015

Parkinson's disease is generated by the loss of dopaminergic neurons that cause motor symptoms. Initial cell therapies utilizing fetal tissues (ventral mesencephalon) have been reported to yield promising results but have ethical concerns and complications [88–92]. Several researchers subsequently started to use hPSC-derived dopaminergic neuron progenitor cells instead of the human fetal ventral mesencephalon for the medical care of patients with Parkinson's disease (PKD).

PKD was first treated in patients by transplantation of dopaminergic neuron (dopamine-secreting) progenitor cells derived from hESCs in China (NCT03119636) in 2015. The dopaminergic neurons of the midbrain are the main source of dopamine secretion in the human central nervous system. Their loss leads to neurological disorder disease of PKD. In 2017, autologous hiPSC-derived dopaminergic neuron progenitors were transplanted into one PKD patient at McLean Hospital in the USA. Following this success, autologous hiPSC-derived dopaminergic

neuron progenitors were transplanted into another 8 patients in 2023 (NCT06687837) [29]. However, no clinical results have been reported.

Park et al. prepared midbrain dopaminergic (mDA) cells from clinical-grade hESCs on a large scale under good manufacturing practice (GMP) conditions [93]. A phase 1/2a clinical trial (NCT05887466) commenced in which 12 patients with PKD were transplanted with 3.15 million (low dose) or 6.3 (high dose) million hESC-derived mDA cells per patient in 2023. From Tabar's work [94], three patients treated with low-dose hESC-derived mDA cells showed an average improvement of 19% (from stage 3.7 to 3.0) according to the Hoehn and Yahr scale, whereas three patients treated with high-dose hESC-derived mDA cells showed a more extensive improvement of 44% according to the Hoehn and Yahr scale (from stage 3.7 to 2.0), which indicates a distinguishable improvement from severe to mild disease states, where the Hoehn and Yahr scale is a key parameter for evaluating the severity of motor symptoms in patients with PKD [95,96].

Schweitzer et al. prepared hiPSCs from a patient's own skin cells (fibroblasts) and differentiated them into dopaminergic cells. Four million or eight million hiPSC-derived dopaminergic cells were transplanted into the putamen on each side of the brain starting in 2014 (NCT06687837) [29]. There is another clinical trial using autologous hiPSC-derived dopaminergic neuron transplantation for PKD starting from 2024 (NCT06422208). However, no results have been reported.

Sawamoto et al. performed clinical trials for patients with PKD using allogeneic hiPSC-derived dopaminergic progenitors (jRCT2090220384) [97], in which seven patients (aged 50–69 years) received bilateral transplantation of allogeneic hiPSC-derived dopaminergic progenitors. Four of the six patients who underwent efficacy evaluation were reported to have improved Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III OFF (unmedicated) scores at 2 years after transplantation, where the MDS-UPDRS part III score was determined through an objective evaluation by neurologists. Furthermore, five patients reported improved ON (with medication) scores. Immunosuppressive medicine was administered to the patients for 15 months. Although they did not include a placebo control in their trials, the transplantation of allogeneic hiPSC-derived dopaminergic progenitors is safe and promising for treating patients with PKD.

2.5. Transplantation of hPSC-Derived MSCs for Medical Care of GvHD, Interstitial Cystitis, Multiple Sclerosis Starting in 2017

One of the most promising effects of adult stem cell transplantation into patients is the medical care of graft-versus-host disease (GvHD) by hBMSC transplantation, in which hBMSCs are one type of MSCs. MSCs contribute to immunosuppression and trophic effects via the secretion of growth factors and cytokines (Figure 2 [98]) [99–102]. MSCs such as hBMSCs, hADSCs, hAFSCs, and hDPSCs typically produce transforming growth factor beta (TGF-β), Interleukin-10 (IL-10), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF) and other trophic factors (cytokines), as shown in Figure 2 [98]. Other researchers have reported that MSCs, such as hBMSCs, also secrete fibroblast growth factor (FGF-2), keratinocyte growth factor (FGF-7, KGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF-2, IGF-1), which promote cell expansion, tissue remodeling, tissue regeneration, and angiogenesis [55,99]; these cytokines can contribute to the regeneration of tissue and organs in patients.

Many (>1000) clinical trials have reported the use of MSCs to treat specific diseases, such as GvHD, COVID-19, cartilage damage, and neurological disorders [99,103]. The most promising application of MSC therapy is GvHD, whereas the effectiveness of MSCs for the treatment of other diseases should be carefully examined.

GvHD is a life-threatening complication that typically occurs after allogeneic tissue or organ transplantation, especially allogeneic stem cell transplantation, such as bone marrow transplantation. The proliferation of MSCs such as BMSCs or ADSCs, which are isolated from human tissues, is limited. Therefore, hPSC-derived MSCs are being generated and are beginning to be utilized in clinical trials for the medical care of patients with GvHD.

The generation of MSCs from hPSCs is valuable for overcoming the disadvantages of MSCs (BMSCs, ADSCs, DPSCs and AFSCs), such as the variability of lot differences originating from different donors and limited cell proliferation (due to the problem of aging) (Figure 3 [104]). In 2017, allogeneic hiPSC-derived MSCs (CYP-001) were transplanted into 15 patients with acute steroid-resistant GvHD (NCT02923375) [54]. The results revealed that hiPSC-derived MSC transplantation suppressed GvHD, and no serious adverse events were reported. Nine of the fifteen patients (60%) were alive at the two-year follow-up, which was higher than the two-year survival of patients receiving standard care [25]. It might be interesting to investigate whether universal hPSC-derived MSCs (universal MSCs) would work to suppress GvHD better than conventional hPSC-derived MSCs and could be used for any patient for the treatment of GvHD and other diseases in the future.

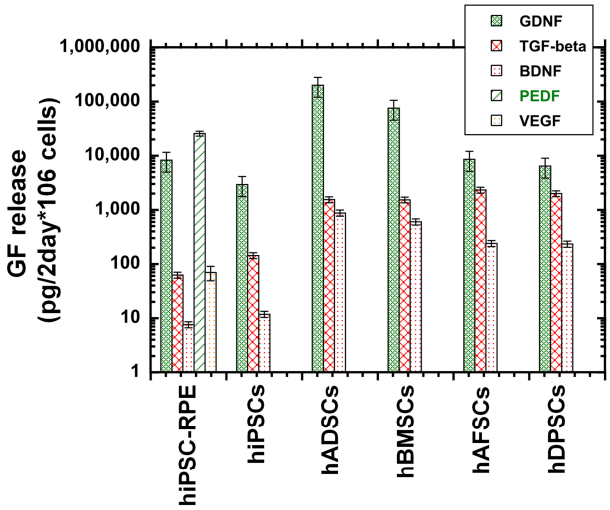

Figure 2. Secretion of the trophic factors VEGF, PEDF, BDNF, TGF-β, and GDNF by hiPSC-derived RPE cells, hiPSCs, hADSCs, hBMSCs, hAFSCs, and hDPSCs, as evaluated by an enzyme-linked immunosorbent assay (ELISA). VEGF, vascular endothelial growth factor; PEDF, pigment epithelium-derived factor; BDNF, brain-derived neurotrophic factor; TGF-β, transforming growth factor-β; GDNF, glial cell line-derived neurotrophic factor. The plot was constructed using previously reported data [98].

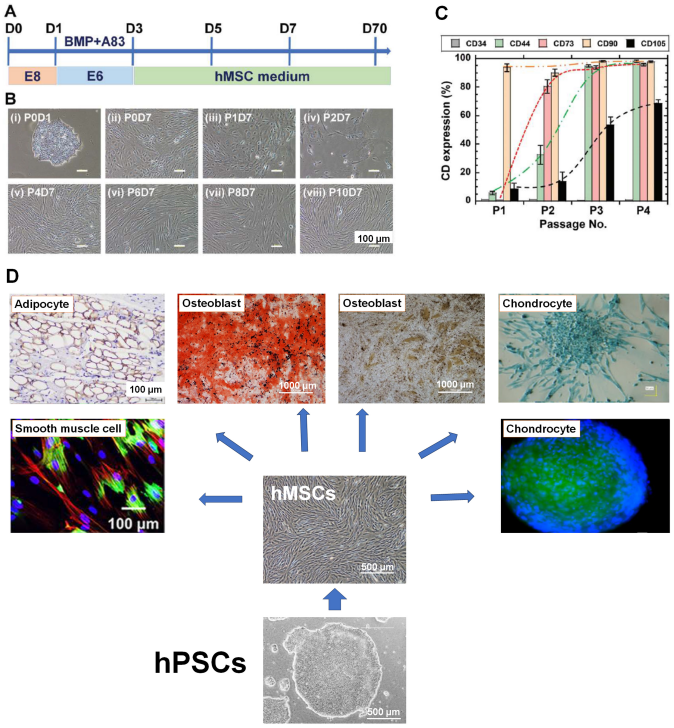

Figure 3. Generation of MSCs from hPSCs. (**A**) Timeline of the protocol to induce hPSCs into hMSCs. (**B**) Morphology of induced cells on day 1 after differentiation (P0D1) (i), day seven (P0D7) (ii), day seven on passage one (P1D7) (iii), day seven on passage two (P2D7) (iv), day seven on passage four (P4D7) (v), day seven on passage six (P6D7) (vi), day seven on passage eight (P8D7) (vii), and day seven on passage ten (P10D7) (viii). (**C**) Dependence of the expression of MSC surface markers (CD105, CD90, CD93 and CD44) and CD34 on the passage number of hESC (H9)-differentiated hMSCs. (**A**–**C**) [104] Copyright 2022. Adapted with permission from The Royal Society of Chemistry. (**D**) General illustration of the induction of hPSCs into hMSCs and the induction of hMSCs into adipocytes, osteoblasts, chondrocytes and smooth muscle cells for clinical application. Adipose cell and chondrocyte pictures were taken from Ref. [105] under a Creative Commons Attribution 4.0 International License.

Three patients with interstitial cystitis were treated with hESC-derived MSCs by the team of a Korean researcher (Dr. Myung-Soo Choo) (NCT04610359). Some patients showed reduced lesion size and pain, although the patient number in this clinical trial was too small to conclude that hESC-derived MSC transplantation is statistically effective for curing the disease [24]. Another group is evaluating intravenous transplantation of hESC-

derived MSCs for the treatment of multiple sclerosis (MS) (NCT04956744). However, no clinical results have been reported for this clinical trial.

2.6. Transplantation of hPSC-Derived Hepatocytes for Medical Care of Liver Failure Starting in 2018

The application of hPSC-derived hepatocytes to cure acute liver failure is relatively difficult. For acute liver failure, hPSC-derived hepatocytes are transplanted into a patient as a bridge treatment before regeneration of patient livers or liver transplantation into the patient. Because hepatocytes are derived from the endoderm lineage, it is relatively difficult to generate mature hepatocytes in large numbers, whereas an estimated 1 to 10 million hepatocytes per patient are needed for transplantation. In 2018, the National Center for Child Health and Development in Japan started a clinical trial in which hESC-derived hepatocytes were transplanted into two neonatal patients with urea cycle disorders (JMA-IIA00412) [29]. In another case, hESC-derived hepatocytes were also transplanted into ten patients with liver failure at Xiangya Hospital of Central South University in China (ChiCTR2100052988) [29]. To date, precise clinical results for both cases have not yet been obtained. It should be interesting to evaluate whether hPSC-derived hepatic progenitor cells and not mature hepatocytes might effectively work for the treatment of patients of chronic (and not acute) liver failure.

2.7. Transplantation of hPSC-Derived NK Cells for Medical Care of Cancer Starting in 2019

NK cells are a type of white blood cells that support the body in fighting infections and disease. NK cells are part of the innate immune system and are often the first line of defense against infection. In 2019, hiPSC-derived NK cells (FT500) without gene editing were started on to be administered to thirty-seven patients with advanced solid tumors (NCT03841110). Engineered hiPSC-derived NK cells, iNK cells (FT596, FT576, FT538, FT522, and FT516), were also administered to patients with blood tumors, such as B-cell lymphoma, chronic lymphocytic leukemia, multiple myeloma and acute myeloid leukemia. Clinical results from these clinical investigations have not been reported, but some press releases and information show promising results in these clinical trials [29]. Notably, these clinical trials are the first to report universal (hypoimmunogenic) hPSC-derived cells that are transplanted into patients for disease treatment in our database research.

In 2022, hiPSC-derived NK (CAR19-iNK) cells with gene editing began to be administered to patients with refractory or relapsed CD19-positive B cell tumors (NCT05336409). This stem cell product is made with gene editing to promote immune evasion through the overexpression of HLA-E and the knockout of major histocompatibility complex (MHC) class II and I (to generate universal cells), including a safety switch, where universal cells can be transplanted into patients with all types of HLA class II and class I, eliciting no immune response by NK cells, macrophages or cytotoxic $CD8^+$ T cells (Figure 4) [106].

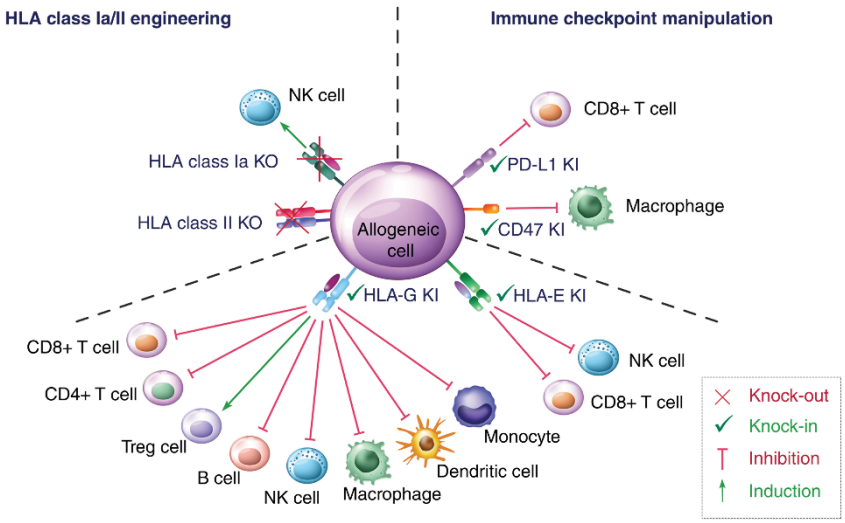

Figure 4. Generation of hypoimmunogenic or universal hPSCs by gene editing. Adapted under a Creative Commons License (CC BY-NC-ND 4.0) [107].

2.8. Transplantation of hPSC-Derived T Cells for Medical Care of Cancer Starting in 2019

The hPSC-differentiated T-cell product FT819, which contains a CD19 CAR insertion in the T-cell receptor (TCR) alpha constant (TRAC) locus for cancer treatment, was reported in 2019 [108,109]. These genetically

modified T cells ignore the endogenous TCR, which helps to reduce the generation of GvHD in patients. A current clinical investigation using hPSC-derived T cells (FT819) was performed for patients suffering relapsed/refractory B-cell lymphoma (NCT04629729).

Clinical investigations using chimeric antigen receptor (CAR)-T cells targeting CD19 (Figure 5) [110–113] have also been conducted in patients suffering B-cell-driven autoimmune disease [114]. hPSC-derived T cells (FT819) were also administered to patients having systemic lupus erythematosus (SLE) in the NCT06308978 clinical trial. Compared with autologous CAR-T or CAR-NK therapy, off-the-shelf hPSC-derived CAR-T cells and CAR-NK cells should be effective for cancer therapy because they are inexpensive and easy to access compared to autologous hiPSC-derived T cells and NK cells.

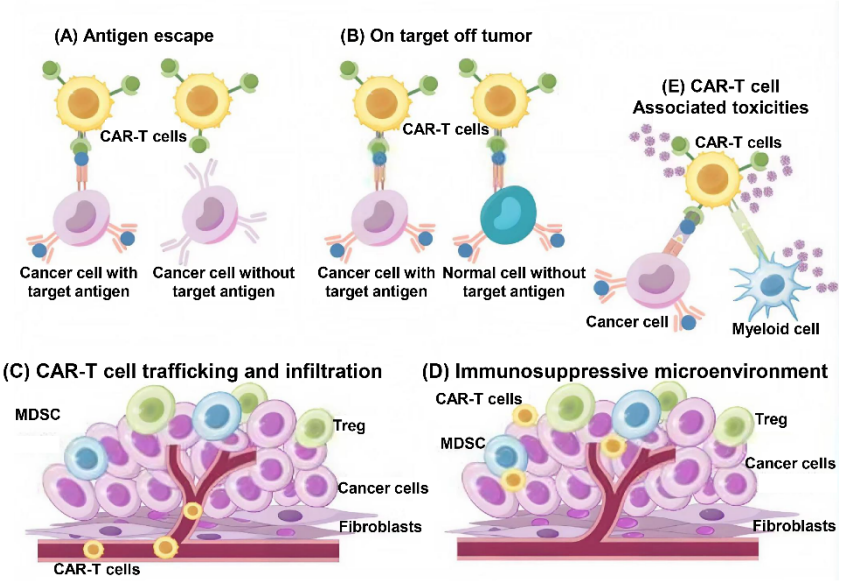

Figure 5. Problems with CAR-T-cell therapy. Current limitations in CAR-T-cell therapy show (**A**) antigen escape, (**B**) on-target off-tumor effect, (**C**) tumor trafficking and infiltration, (**D**) the tumor environment of immunosuppression, and (**E**) toxicities related to CAR-T cells.

2.9. Transplantation of hPSC-Derived Neural Stem Cells (NSCs) for Medical Care of Stroke Starting in 2021

In 2021, Stanford University started to administer hESC-derived neural stem cells (NSCs) for the treatment of ischemic subcortical stroke (https://med.stanford.edu/news/all-news/2021/09/grants-for-stem-cell-clinical-trials.html). The outcome of these clinical trials was that in early 2023, at six months, the first six transplanted patients were tolerating the treatment well [29]. Another clinical trial using NSC administration was performed for the care of Huntington's disease by Leslie Thompson and his group at the University of California Irvine in 2024 [29]. To date, no clinical results have been reported from these trials. However, preclinical studies have indicated that NSC transplantation is expected to suppress endogenous accumulation of mutant Huntingtin and promote the generation of neurotrophic factors, supporting the results of experiments in animal disease models [115,116].

2.10. Transplantation of hPSC-Derived Neurons for Medical Care of Focal Epilepsy Starting in 2022

Focal epilepsy expresses a neurological condition where the extensive symptom is recurring seizures affecting one hemisphere of the patient's brain. Focal epilepsy is generated by episodes of uncontrollable hyperactivity of excitatory neurons in isolated subregions of the brain, resulting in the appearance of spasms and motoric seizures in neuronal discharge [29]. The transplantation of hESC-differentiated inhibitory GABAergic interneurons was conducted into the epileptic focus of the brains, which restricted the hyperactivity of neurons and suppressed seizure occurrence in animal (mouse) models of genetic epilepsy or mesothelial temporal lobe epilepsy (MTLE) [117].

In 2022, investigators transplanted the interneuron product NRlX-1001 (hESC-differentiated inhibitory GABAergic interneurons) into the first patient in a clinical trial (NCT05135091) on drug-resistant MTLE. They reported that four out of five patients transplanted with a low initial amount of NRlX-1001 displayed a more than 50% decrease in seizures and that three patients did not express their most disabling types of focal seizures [29]. In particular, two patients experienced a greater than 95% reduction in the number of seizure episodes at the 1–2-

year follow-up. These results indicate that allogeneic human neurons can survive and function in patient brains in the long term with and without immunosuppressive treatment. In this trial, immunosuppressive medicine was not used for the patients one year after transplantation [29].

3. Conclusions

Currently, only around 150 cases have reported for clinical application using hPSC-differentiated cells, whereas approximately 10,000 cases are reported for clinical application using adult stem cells, mainly using BSCs and ADCs. This is because hPSC-differentiated cells may cause the generation of tumors. Universal cells are attractive cell source for the transplantation of hPSC-differentiated cells, because off-the-shelf types of hPSC-differentiated cells can be provided on market. However, universal cells are more easily to generate tumors on patients because of immune reaction escape on the patients. We believe that the clinical application using hPSC-differentiated cells will be in popular in near future.

Author Contributions

A.H.: Conceptualization, visualization, methodology, writing, funding acquisition, supervision, and revising the manuscript; T.W. and X.K.: Figure drawing; Z.T. and T.-C.S.: Data collection, and data analysis. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data Availability Statement

All relevant data are available within the article or from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

Parts of the Graphic Abstract were made by Nano Banana (https://nanobananapro.com/) from the authors' concept of the illustration to generate the Graphic Abstract. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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