NEURAL REGENERATION RESEARCH
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Review

Stem cell repair strategies for epilepsy

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https://doi.org/10.4103/NRR.NRR-D-24-01337

Date of submission: November 9, 2024

Date of decision: December 25, 2024

Date of acceptance: January 22, 2025

Date of web publication: June 19, 2025

From the Contents

Abstract

Epilepsy is a serious neurological disorder; however, the effectiveness of current medications is often suboptimal. Recently, stem cell technology has demonstrated remarkable therapeutic potential in addressing various neurological diseases, igniting interest in its applicability for epilepsy treatment. This comprehensive review summarizes different therapeutic approaches utilizing various types of stem cells. Preclinical experiments have explored the use and potential therapeutic effects of mesenchymal stem cells, including genetically modified variants. Clinical trials involving patient-derived mesenchymal stem cells have shown promising results, with reductions in the frequency of epileptic seizures and improvements in neurological, cognitive, and motor functions reported. Another promising therapeutic strategy involves neural stem cells. These cells can be cultured outside the body and directed to differentiate into specific cell types. The transplant of neural stem cells has the potential to replace lost inhibitory interneurons, providing a novel treatment avenue for epilepsy. Embryonic stem cells are characterized by their significant capacity for self-renewal and their ability to differentiate into any type of somatic cell. In epilepsy treatment, embryonic stem cells can serve three primary functions: neuron regeneration, the maintenance of cellular homeostasis, and restorative activity. One notable strategy involves differentiating embryonic stem cells into γ-aminobutyric acidergic neurons for transplantation into lesion sites. This approach is currently undergoing clinical trials and could be a breakthrough in the treatment of refractory epilepsy. Induced pluripotent stem cells share the same genetic background as the donor, thereby reducing the risk of immune rejection and addressing ethical concerns. However, research on induced pluripotent stem cell therapy remains in the preclinical stage. Despite the promise of stem cell therapies for epilepsy, several limitations must be addressed. Safety concerns persist, including issues such as tumor formation, and the low survival rate of transplanted cells remains a significant challenge. Additionally, the high cost of these treatments may be prohibitive for some patients. In summary, stem cell therapy shows considerable promise in managing epilepsy, but further research is needed to overcome its existing limitations and enhance its clinical applicability.

Key Words: astrocyte transdifferentiation; cell therapy; cell transplantation; clinical trials; embryonic pluripotent stem cells; epilepsy; gamma-aminobutyric acidergic neuron; induced pluripotent stem cells; mesenchymal stem cells; nerve regeneration; neural stem cells; organoid

Introduction

Epilepsy is a common neurological disorder characterized by recurrent seizures that are caused by abnormal electrical activity in the brain (Jiao et al., 2025; Liu et al., 2025). According to the latest statistics from the World Health Organization, approximately 51 million individuals worldwide are affected by this condition (Thijs et al., 2019; Asadi-Pooya et al., 2023). The prevalence rate of active epilepsy is 0.64%, with about 4.9 million new cases diagnosed each year (Asadi-Pooya et al., 2023). Despite the continuous emergence of new antiepileptic drugs (AEDs), over 30% of patients with epilepsy globally live without effective control measures, including those with a condition known as drug-resistant epilepsy (DRE) (Patil et al., 2024; Qiu et al., 2024). Effectively addressing DRE (Waris et al., 2024b), while concurrently exploring the underlying causes of epilepsy and developing innovative antiepileptic therapies, constitutes one of the most pressing challenges that neuroscience must resolve (Manford, 2017).

Temporal lobe epilepsy (TLE) is the most prevalent form of DRE in adults, affecting about 70% of patients. These individuals often experience the rapid progression of the condition, marked by poor seizure control, cognitive decline, and behavioral disturbances (Sharma et al., 2024). Hippocampal sclerosis (HS), a hallmark of DRE, is characterized by the loss of pyramidal cells, proliferation of astrocytes, reorganization of dentate granule cell axons, and dispersion of granule cells (Middlebrooks et al., 2024). These structural alterations lead to the abnormal synchronization and increased excitability of neurons, resulting in the aberrant discharge of signals within the hippocampus that ultimately trigger seizures (Scharfman, 2024). Traditional AEDs primarily target seizure control but do not address the underlying brain pathology associated with epilepsy, which may significantly contribute to drug resistance and the various complications of DRE.

The causes of drug resistance in DRE are multifaceted and not yet fully understood. Several mechanisms are believed to contribute to the development and progression of DRE. One theory, known as the "drug target hypothesis," suggests that seizures can alter targets in the brain that AEDs act upon, making the medications less effective (Auvin et al., 2023). Another theory, the "drug transporter hypothesis," proposes that the blood–brain barrier in the epileptic foci of DRE patients has increased levels of transporter proteins that pump AEDs out of the brain, thereby reducing the effective concentration of the medication at the epileptic site (Löscher and White, 2023). A third theory, the "pharmacokinetic hypothesis," posits that organs such as the small intestine and liver overexpress these transporter proteins in DRE patients, lowering the overall levels of medication in the body and reducing the amount that reaches the brain (Fonseca-Barriendos et al., 2022). Additionally, factors such as genetic mutations, epigenetic modifications, neuroinflammation, and blood–brain barrier disruption may also contribute to drug resistance in DRE (Löscher et al., 2020).

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Funding: *This work was supported by the National Natural Science Foundation of China, Nos. 82471471 (to WJ), 82471485 (to FY); Shaanxi Province Special Support Program for Leading Talents in Scientific and Technological Innovation, No. tzjhjw (to WJ); Shaanxi Key Research and Development Plan Project, No. 2023-YBSF-353 (to XW); the Joint Fund Project of Innovation Research Institute of Xijing Hospital, No. LHJJ24JH13 (to ZS).*
How to cite this article: *Ma X, Wang Z, Niu Y, Zhao J, Wang X, Wang X, Yang F, Wei D, Sun Z, Jiang W (2026) Stem cell repair strategies for epilepsy. Neural Regen Res 21(4):1428-1446.*

Despite the introduction of over 30 types of AEDs in the past three decades, the prevalence of DRE has not decreased, with approximately one-third of epilepsy patients consistently developing this condition (Klein et al., 2024).

Seizures are induced by transient paroxysmal and hypersynchronous discharges within the brain resulting from an imbalance between excessive neuronal excitation and insufficient inhibition in regions of abnormal discharge (Gettings et al., 2025). Neuronal activity is modulated by a variety of neurotransmitters, with gamma-aminobutyric acid (GABA) serving as the principal inhibitory neurotransmitter in the cerebral cortex (Zhang et al., 2024b). GABA is primarily found in short-range interneurons and helps maintain signal balance by forming connections between neuronal bodies and nearby axons, counteracting overexcitation (Treiman, 2001). When this delicate equilibrium is disrupted, seizures can occur. Consequently, augmenting GABAergic neurons in the hippocampus through stem cell transplantation is emerging as a critical strategy for restoring the proper balance between excitation and inhibition in the brain, potentially offering a solution for DRE.

In recent years, the rapid development of stem cell technology has provided new hope for the treatment of epilepsy (**Figure 1**). Stem cells are recognized for their significant capacity to differentiate into various cell types in humans and animals. Unlike specialized cells, these stem cells can proliferate numerous times, producing millions of cells. They play crucial roles in the repair and regeneration of the central nervous system, influencing the pathophysiological processes of epilepsy through mechanisms such as the secretion of neurotrophic factors, modulation of inflammatory responses, and neuronal regeneration (Lybrand et al., 2020). Current research on stem cell therapies for epilepsy primarily focuses on several cell types, including mesenchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs).

Epilepsy can cause permanent damage to neural cells, but stem cell–based therapies, such as the transplantation and injection of exosomes derived from MSCs, exhibit remarkable potential for repair (Pegtel and Gould, 2019). Convincing empirical evidence from both experimental and clinical trials robustly supports their satisfactory safety and repair efficacy (Wu et al., 2023). In epilepsy, the process of hippocampal neurogenesis is disrupted (Toda et al., 2019), particularly during prolonged seizures, leading to a depletion of NSCs. Consequently, the transplantation of NSCs can improve seizure frequency, learning and memory impairments, and the persistence of depression (Geribaldi-Doldán et al., 2023). Another area of research involves the use of human ESCs. These cells, derived from the inner cell mass of embryos (Rivron et al., 2018), can be artificially maintained and propagated in an undifferentiated state before being directed toward a specific differentiation pathway (Whiting et al., 2015). The development of strategies to guide their differentiation into specific types of neurons and glia is now providing hope for a potential stem cell-based cure for hippocampal sclerosis in epilepsy (Shahbazi and Pasque, 2024). Advances in stem cell research, such as the development of iPSCs by Takahashi and Yamanaka (2006), have opened up new possibilities for treating epilepsy. By reprogramming somatic cells back to a pluripotent state, researchers can create patient-specific models to study the disease *in vitro* (Javaid et al., 2022).

In this review, we summarize the various stem cell–based therapies, discuss foundational and clinical studies, and explore future directions in epilepsy treatment. Our aim is to highlight the potential benefits of stem cells in managing epilepsy and improving patient outcomes.

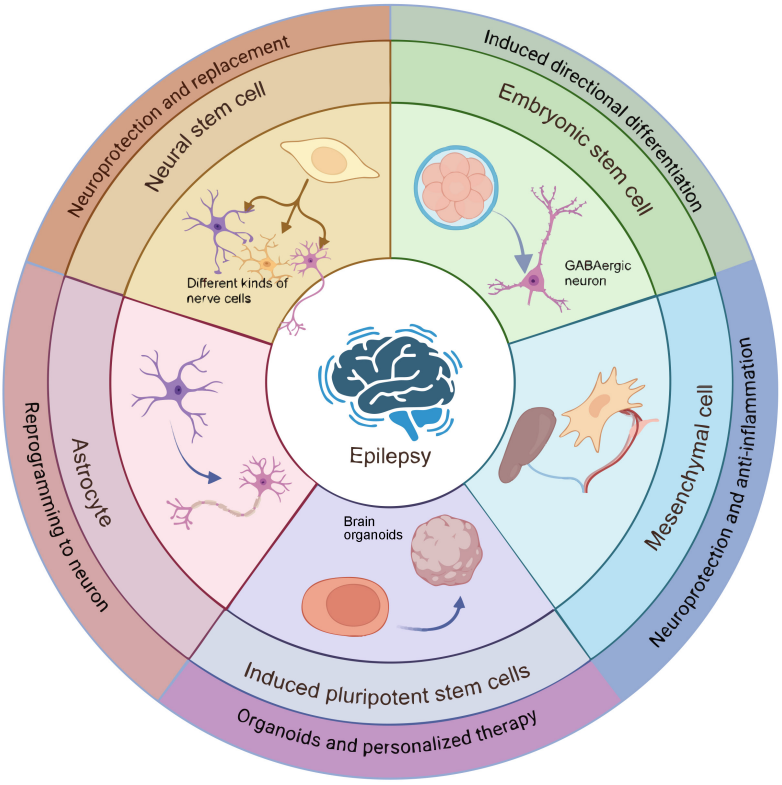

Figure 1 | **A pie chart overview of mechanisms of stem cell therapy for epilepsy.**
Mesenchymal stem cells primarily exert their therapeutic effects through nutritional support, producing extracellular vesicles and growth factors. Preclinical and clinical trials have demonstrated that patient-derived mesenchymal stem cells can reduce seizure frequency. Neural stem cells secrete neurotrophic factors such as brain-derived neurotrophic factor and glial cell line derived neurotrophic factor, possess immunomodulatory effects, and can be directed to differentiate into specific cell types *in vitro*. Transplanting neural stem cells can replace lost inhibitory interneurons, offering a potential treatment for epilepsy. Embryonic stem cells exhibit remarkable self-renewal and differentiation potential, enabling neuron regeneration, the maintenance of cellular homeostasis, and restorative therapies. Differentiating embryonic stem cells into γ-aminobutyric acidergic neurons for transplantation is a promising strategy in clinical trials for refractory epilepsy. Induced pluripotent stem cells, sharing the same genetic background as the donor, reduce immune rejection and ethical concerns. They allow for the creation of patient-specific neurons for disease modeling and drug testing. Additionally, induced pluripotent stem cells-derived organoids are revolutionizing regenerative medicine, while research into astrocyte reprogramming shows potential but remains controversial. Created with BioRender.com.

Search Strategies

The primary databases utilized for the computer-based searches included PubMed, Web of Science, Embase, and the Cochrane Library. We used a combination of subject headings and free-text terms related to "epilepsy," "stem cell," and "cell transplantation" for our search, without applying any language restrictions. Our focus was on identifying relevant literature discussing the use of stem cell transplantation for epilepsy treatment, with particular emphasis on four specific types of stem cells: MSCs, NSCs, ESCs, and iPSCs. We prioritized literature published within the last 3 years. After an initial screening to ensure the retrieved literature was relevant, we conducted in-depth reading and analysis, extracting key information to support the writing of a comprehensive review or research report. The majority of the selected literature (76.5%) was published between 2018 and 2024.

Epilepsy

Pathophysiology

Epilepsy is a chronic condition characterized by paroxysmal abnormal discharges of neuronal populations in the brain resulting from an imbalance between excitatory and inhibitory activities (Adeyeye et al., 2024). This imbalance leads to excessive, hypersynchronous, and oscillatory neuronal activity, which impairs normal brain function.

The etiologies of epilepsy are diverse (Sveinsson et al., 2023) and are often associated with factors such as head trauma, infections, and tumors. Larivière et al. (2024), who investigated the links between drug-resistant TLE and hippocampal pathology, revealed that the widespread pathology of TLE may extend into brain networks associated with the hippocampal core. During seizures,

patients may experience episodic disturbances in motor, sensory, consciousness, psychological, and autonomic functions, which can be life-threatening when accompanied by respiratory or cardiac arrest and may ultimately lead to sudden unexpected death (Gu et al., 2024). Epilepsy is also associated with cognitive, behavioral, psychological, and social impairments in patients. The interplay between mental health conditions and epilepsy is bidirectional and complex. Common mental health disorders linked to epilepsy include depression and anxiety, which can significantly affect patients' quality of life (Tarrada and Hingray, 2024). Additionally, epilepsy often co-occurs with other physical health issues such as type 1 diabetes, arthritis, and gastrointestinal ulcers (Yuen et al., 2018), posing a substantial burden on society and healthcare systems.

Treatment

Drug treatment

For many years, AEDs have been pivotal in the treatment of epilepsy by providing significant relief to patients (**Figure 2**). Their core action is to modulate neuronal excitability and disrupt the abnormal electrical signals in the brain (Ghosh et al., 2023). The introduction of AEDs marked a significant advancement in epilepsy management, leading to improved disease control and enhancing patients' quality of life. There are various types of AEDs (e.g., phenytoin, carbamazepine, valproate, lamotrigine, and levetiracetam), each targeting specific mechanisms to control seizures (Yuen et al., 2018; Waris et al., 2024a). Doctors select the most suitable AED based on individual patient factors.

AEDs have limitations that make managing epilepsy challenging. Some traditional AEDs can cause side effects, such as cognitive impairments, mood disorders, and systemic toxicity (Löscher et al., 2020). Despite relying on medications such as diazepam, lamotrigine, levetiracetam, and perampanel to control seizures and mitigate long-term damage to brain function, approximately one-third of patients do not respond well to these treatments (Löscher et al., 2020) and may experience adverse effects. Additionally, DRE complicates treatment; patients' varying physiologies can lead to different disease manifestations and drug resistance, rendering traditional therapies ineffective in some cases.

Traditional therapies still hold a foundational position in epilepsy management, and further research on individual drug resistance and tolerance is needed to enhance these therapies. In recent years, a newly approved AED, cenobamate, has demonstrated significant antiepileptic potential in its ability to inhibit sodium currents and enhance GABA-mediated effects. Clinical trials have shown that cenobamate can effectively reduce epileptic seizures. Additionally, it possesses neuroprotective properties that may alter the course of epilepsy (Löscher et al., 2020; Błaszczyk et al., 2024). The development of new targets and drugs is expected to greatly advance drug therapy in this field.

Surgical treatment

The second-best option for treating focal DRE is surgery to remove the part of the brain causing the seizures. This approach is highly effective when epileptic seizures originate from specific brain regions, such as in TLE (Waris et al., 2024b). In addition to lesion resection in epilepsy with identifiable causes, several established and effective resection surgeries exist, including temporal lobectomy, frontal lobectomy, insula lobectomy, parietal lobectomy, occipital lobectomy, functional hemispherectomy, and corpus callosotomy. The different resection methods vary in terms of surgical indications and prognoses (Vakharia et al., 2018). However, surgical treatment carries risks such as subdural hemorrhage, cerebral edema, and neurological impairments, making it a last resort (Rugg-Gunn et al., 2020). A previous study showed that patients diagnosed with frontobasal epilepsy who undergo surgery early, exhibit positive magnetic resonance imaging results, and have tumors as the cause of their seizures are the most likely population to achieve freedom from seizures (Grote et al., 2024). However, various less invasive alternatives to surgery have emerged, including neuromodulation, ablation procedures, and stereotactic radiosurgery. The latter stands out as a non-invasive option particularly suitable for patients with medical conditions that elevate surgical risks, those with epileptogenic foci located in the functional cortex, non-responders to surgical interventions, patients who decline surgery, and those facing geographical constraints in accessing epilepsy centers. However, it also carries certain risks that necessitate ongoing medical supervision to prevent potential complications such as delayed cerebral edema, visual field impairments, and radiation-induced necrosis (Daly et al., 2024).

Neuromodulation treatment

Traditional AEDs have been the cornerstone of epilepsy treatment for many years; however, a significant number of patients still experience seizures despite receiving this therapy. This has stimulated the exploration of new treatments to address the unmet medical needs of patients with DRE. Neuromodulation therapy is a treatment approach that uses various types of stimulus to modify the function or state of the nervous system with the aim of improving health outcomes (Piper et al., 2022). The key idea behind this therapy is to apply a stimulus that helps reduce the overactivity of brain cells and decrease abnormal electrical signals, thereby reducing the frequency of epileptic seizures (Samanta et al., 2024).

Neuromodulation therapies include deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation (Ryvlin et al., 2021). Deep brain stimulation involves implanting electrodes into specific nuclei deep in the brain to regulate nervous system function through electrical stimulation; however, it is a highly invasive procedure (Adin et al., 2021). Vagus nerve stimulation helps to control epilepsy by stimulating the vagus nerve via a battery that sends weak electrical pulses; however, it carries the risk of injuring nearby nerves. Transcranial magnetic stimulation utilizes magnetic fields to target the cerebral cortex, although its effectiveness in treating epilepsy remains unclear (Somaa et al., 2022; Vucic et al., 2023). Consequently, there is a pressing need for studies focusing on the development of new therapeutic methods to address the challenges of epilepsy treatment.

In recent years, a novel hippocampal stimulation method, known as sequential neuro-focusing (SNF), has emerged as a promising approach for managing TLE. SNF uses a sequence of precisely organized microstimulation pulses to effectively terminate seizures while minimizing the potential side effects associated with edge field stimulation. Compared to the conventional wide-field stimulation method, SNF demonstrates superior safety and efficacy, significantly reducing unwanted

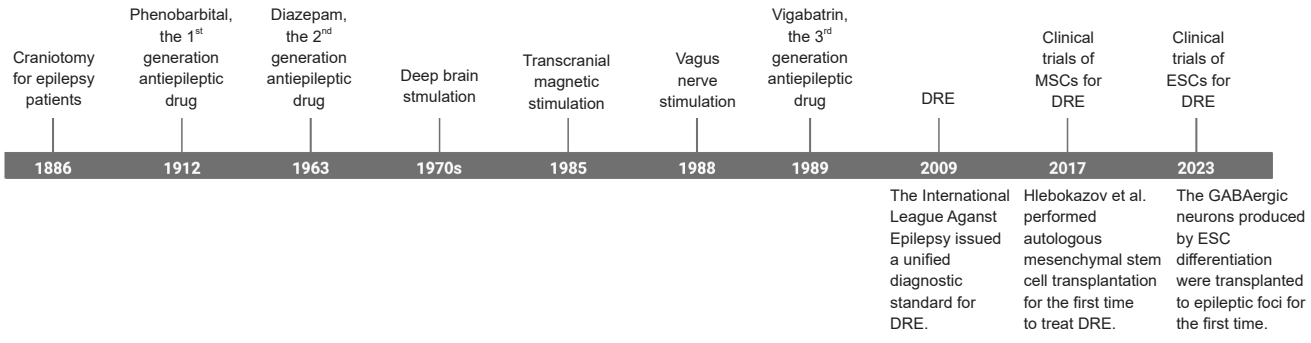

Figure 2 | **A timeline outlining key milestones in the development of therapies for epilepsy with a focus on DRE and stem cell treatment.**
The recognition of drug resistance as a significant challenge marked a turning point in epilepsy treatment. Since then, research has explored the potential of various types of stem cells. Clinical trials have assessed the safety and efficacy of mesenchymal stem cells in treating DRE. The timeline highlights the progress in this field, underscoring the promising role of ESCs in advancing epilepsy therapy. Created with BioRender.com. DRE: Drug-resistant epilepsy; ESCs: embryonic stem cells.

neural activity. Kang et al. (2022) showed that SNF can disrupt epileptic rhythms and effectively control TLE seizures, an outcome not consistently achieved with traditional wide-field stimulation. Ongoing research into alternative therapies for epilepsy, such as cannabidiol, the ketogenic diet, gene therapy, and optogenetic therapy, holds promise for patients (Ghosh et al., 2023). Additionally, emerging findings suggest there is a strong link between epileptic seizures and nitrogen imbalance within the gut microbiota, indicating that targeting the gut microbiota may offer a novel therapeutic avenue for epilepsy treatment (Wei et al., 2023).

Progress in Stem Cell Use for Epilepsy Therapy

Classifications

Stem cells are primarily classified into four distinct categories based on their source of origin (Ke et al., 2024). The first category includes MSCs, which can be obtained from bone marrow or adipose tissue. The second category comprises NSCs, derived from neural tissue and classified as adult stem cells. The third category consists of ESCs, which are isolated from embryonic gonadal ridges or purified from teratocarcinoma cells. Lastly, there are iPSCs, which can be modified to exhibit characteristics similar to ESCs through genetic reprogramming techniques (Kolios and Moodley, 2013; Chang and Chang, 2022; **Figure 3**).

Mesenchymal stem cells

MSCs are present in nearly all tissues in the body and possess the abilities of self-renewal and differentiation into various cell types. In the context of epilepsy treatment, the clinical value of MSCs primarily derives from their paracrine properties (Ma et al., 2014), particularly their capacity to produce extracellular vesicles such as exosomes, as well as various cytokines and growth factors. Prior research of an MSC therapy for epilepsy indicates the intravenous infusion of cells and resulted in a significant reduction in seizure frequency. Neuronal survival in the hippocampus of rats with status epilepticus (SE) was observed, along with the preservation of cognitive function (Fukumura et al., 2018). These findings have provided a foundation for further investigations into MSC therapies for epilepsy (Mohammed et al., 2014).

Preclinical experiments with mesenchymal stem cells

Various types of MSCs, including genetically modified MSCs, have been used in preclinical experiments to investigate their potential therapeutic effects. For instance, the transplantation of MSCs with adenosine kinase (ADK)-knockout into rats with TLE resulted in a reduction in seizure frequency, decrease in neuronal apoptosis, and improvement in spatial memory (Zhou et al., 2024a). Another study demonstrated that the transplantation of autologous MSCs secreting interleukin-13 did not alter neuroinflammatory responses or lead to cell loss (Ali et al., 2017). Additionally, human umbilical cord-derived MSCs effectively ameliorated hippocampal damage and glial cell activation (Huang et al., 2016). The transplantation of human umbilical cord–derived blood mononuclear cells has also been shown to have antiepileptic and neuroprotective effects (Costa-Ferro et al., 2014). Moreover, the transplantation of olfactory mucosa-derived MSCs in epileptic mice improved cognitive, motor, and sensory functions, and reconstructed neural networks (Liu et al., 2023).

MSC-derived exosomes rich in microRNA (miRNA) have also played a significant role in MSC treatment for epilepsy. Specifically, exosomes loaded with miR-129-5p can prevent neuronal degeneration by inhibiting the pro-inflammatory HMGB1/TLR4 signaling axis (Liu et al., 2024). MSC-exosome therapy has been found to improve inflammation-induced changes in astrocytes, such as reactive proliferation, inflammatory responses, abnormal calcium signal transduction, and mitochondrial dysfunction. This therapy also reduces learning and memory disorders (Farahmand et al., 2024). Furthermore, exosomes can restore the activation of A1 astrocytes by regulating the Nrf2-NF-κB signaling pathway, indicating their potential as nano-therapeutic agents for treating epilepsy, particularly in association with pathological changes in hippocampal astrocytes (Xian et al., 2019). Neuroinflammation is increasingly being recognized as a pivotal pathological process in various neuropsychiatric disorders, acting either as a primary causative factor or as a secondary response to alterations in brain function (Ravizza et al., 2024). Given their properties, MSCs hold promise for the treatment of inflammatory disorders, including epilepsy.

Clinical trials of mesenchymal stem cells

MSCs are ubiquitous and can be extracted from a diverse array of tissues, including neural tissue, adipose tissue, bone marrow, amniotic fluid, umbilical cord, placenta, menstrual blood, and even dental pulp (Rosen and MacDougald, 2006). Unlike ESCs and iPSCs, MSCs do not lead to ethical dilemmas, teratoma formation, or challenges related to tissue compatibility. Consequently, MSCs are increasingly being considered for clinical applications and have demonstrated promising results across various therapeutic settings. Some of the recent clinical applications of MSCs are listed in **Table 1**.

To avoid immune rejection in stem cell transplant clinical trials, autologous cells derived from MSCs, such as autologous bone marrow nucleated cells (BMNCs) and bone marrow-derived MSCs, are often transplanted into patients (Hlebokazov et al., 2021). Following transplantation, a reduction in seizure frequency has been observed, along with improvements in patients' quality of life and cognitive function. This indicates the potential of stem cell transplantation as a treatment option for patients with DRE. In a study of individuals with TLE accompanied by HS, electroencephalogram (EEG) readings following the intra-arterial administration of autologous BMNCs through the posterior cerebral artery indicated a notable reduction in theta band activity and spike density (DaCosta et al., 2018). This treatment resulted in 40% of recipients having a seizure-free status 6 months after transplantation. The direct delivery of MSCs or MSC-derived autologous cells, either intrathecally or intravenously, has also shown potential in reducing seizure frequency (Hlebokazov et al., 2017) and improving neurological, cognitive, and motor functions in patients with DRE (Szczepanik et al., 2020; Milczarek et al., 2024).

Side effects are an important consideration that cannot be overlooked in clinical trials. While innovative MSC injection therapies offer hope for breakthroughs in epilepsy treatment, researchers must comprehensively and cautiously assess the potential side effects of this technology as it advances toward practical clinical applications (Mesa Bedoya et al., 2024). During trials involving the infusion of MSC-derived stem cells, side effects were relatively common but typically mild. In intra-arterial injection studies, 20% of patients reported headaches the day after the procedure, and one patient experienced postictal psychosis during video-EEG monitoring, which was successfully treated with clobazam (DaCosta et al., 2018).

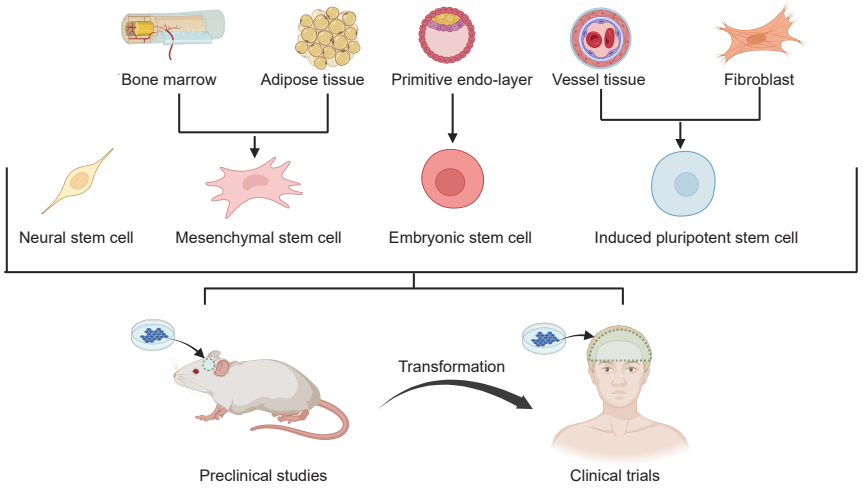

Figure 3 | **Stem cell therapy for epilepsy.**
This image illustrates various types of stem cells used in the treatment of epilepsy. The stem cells depicted include neural stem cells, mesenchymal stem cells derived from bone marrow or adipose tissue, embryonic stem cells extracted from the endoderm, and induced pluripotent stem cells reprogrammed from vascular endothelial cells and fibroblasts. Stem cell therapy has shown promising results in animal models for epilepsy treatment and is gradually advancing to clinical trials. Created with BioRender.com.

Table 1 | **Clinical trials of MSCs for epilepsy**

Type of clinical trials	Disease situation	Cases (*n*)	Cell origin	Route of medication	Curative effect	Side effect	Reference
Single arm test/phase I	Near-middle TLE unilateral hippocampal sclerosis	20	Autologous BMMCs	Arterial infusion	Seizures were significantly reduced at 3 and 6 mon after treatment.	Four patients had a headache on the day after the procedure, and one patient had postictal psychosis.	DaCosta et al., 2018
Single arm test/phase I	Children with DRE	4	Autologous BMNCs	Intrathecal and intravenous injection	The number of seizures decreased and cognitive function improved.	A slight elevation of body temperature to 38°C in all treated children after transplantation.	Milczarek et al., 2018
Phase I/II	DRE	67	Autologous mesenchymal stem cells	Intrathecal and intravenous injection	The paroxysmal epileptic activity decreased and the anxiety and depression scores improved.	No severe adverse effects were observed after cell injections.	Hlebokazov et al., 2021
Controlled experiment/phase I	DRE	10	Autologous mesenchymal stem cells	Intrathecal and intravenous injection	The frequency of seizures decreased significantly.	A single patient reported experiencing a headache that resolved within 2 d without the use of medication.	Hlebokazov et al., 2017
Single arm test/phase I	Autoimmune refractory epilepsy	6	Autologous adipose-derived regenerative cells	Intrathecal injection	The frequency of seizures decreased, and the activity and communication ability improved.	All patients except one had mild side effects such as bruises and febrile.	Szczepanik et al., 2020
Controlled experiment/phase I	DRE	14	Autologous BMNCs and bone marrow mesenchymal stem cells	Intrathecal and intravenous injection	Seizures and status quo decreased, the dosage of anti-seizure medications decreased, and motor function improved.	About 80% patients had at least one adverse event, all of which were mild or moderate.	Milczarek et al., 2024

Table 1 summarizes the basic information, key steps, and results of recent clinical trials involving the transplantation of MSCs in patients with epilepsy, offering a clear and accessible overview for analysis. BMMCs: Bone marrow mononuclear cells; BMNCs: bone marrow nucleated cells; DRE: drug-resistant epilepsy; MSCs: mesenchymal stem cells; TLE: temporal lobe epilepsy.

In an intrathecal injection study, most patients experienced mild side effects, such as bruising, pain at the liposuction site, or febrile reactions lasting 1–2 days (Szczepanik et al., 2020). Similarly, in an intravenous-intrathecal injection study involving autologous BMNC transplantation for children with DRE, all treated children experienced a slight elevation in body temperature, reaching up to 38°C (Milczarek et al., 2018). In two studies by Hlebokazov et al. (2017, 2021), a single patient reported a headache that resolved within 2 days without medication after the transplantation of autologous MSCs. Additionally, when autologous BMNCs and bone marrow-derived MSCs were transplanted, approximately 80% of patients experienced at least one adverse event, all of which were classified as mild or moderate (Milczarek et al., 2024). Overall, the side effects of MSC transplantation appear to be limited and manageable.

MSCs have been extensively studied in clinical trials (Milczarek et al., 2018, 2024), providing valuable insights into their mechanisms, safety, and efficacy in the treatment of epilepsy. These trials have established a solid foundation for future research and clinical applications of MSCs in this field (Alayli et al., 2023). The therapeutic potential of MSCs in epilepsy arises from their ability to increase the density of GABAergic interneurons in the hippocampus and inhibit mossy fiber sprouting (Cao et al., 2022). By enhancing the release of inhibitory neurotransmitters and limiting the abnormal innervation of the dentate inner molecular layer by mossy fibers, MSC treatment may help restrict the spread of epileptic activity and reduce seizure frequency.

MSCs possess remarkable regenerative properties. Following cell or tissue injury, they can be activated by inflammatory cytokines, migrate to the site of damage, and regulate the tissue regeneration process. This is achieved through the release of various factors that facilitate the differentiation and proliferation of progenitor cells while inhibiting inflammatory responses (Nitzsche et al., 2017). In the early stages of inflammation, MSCs detect pro-inflammatory signals through receptors for interleukin-1β, interferon-γ, toll-like receptors, and tumor necrosis factor-α. Initially, they enhance inflammation by secreting chemokines such as C–X–C motif ligand 9, macrophage inflammatory protein-1, C–C motif ligand 5, and C–X–C motif ligand 10, which promote T-cell activation and recruit additional lymphocytes (Salari et al., 2020). MSCs' anti-inflammatory properties and ability to replenish GABAergic interneurons make them a promising candidate for epilepsy treatment.

Although the Food and Drug Administration (FDA) has not yet approved any new drugs specifically involving MSCs for the treatment of epilepsy, the potential of MSCs in addressing nervous system diseases is increasingly being recognized. For instance, on October 26, 2024, the FDA approved NR-20201, the world's first drug derived from allogeneic adipose-derived MSCs (AD-MSCs), for use in clinical trials aimed at treating acute ischemic stroke (de Celis-Ruiz et al., 2022). While this indication differs from epilepsy, it falls within the broader category of nervous system diseases, addressing the promising application prospects and research value of MSCs in this field.

Neural stem cells

NSCs are immature cells with the ability to self-renew and differentiate into various types of brain cells, including astrocytes, oligodendrocytes, and multiple phenotypic neurons. A promising therapeutic strategy utilizing NSCs involves expanding them *ex vivo*, i.e., outside the body, followed by their directed differentiation. This approach aims to convert exogenous neural cells directly into neurons within the body. NSCs can be expanded from different regions of the brain, as well as from human embryonic stem cells (hESCs) and iPSCs. These expanded cells can then be transplanted into the human body using methods such as intravenous injection.

Enhancing inhibitory neurotransmission

Transplantation with NSCs has the potential to replace lost inhibitory interneurons, offering a promising treatment for epilepsy. When NSCs are transplanted into the epileptic hippocampus, they can differentiate into GABAergic interneurons, oligodendrocytes, and astrocytes, all of which secrete antiepileptic factors (Chu et al., 2004). This process increases the number of new inhibitory GABA-positive interneurons that can synthesize the inhibitory neurotransmitter GABA. By enhancing inhibitory neurotransmission, this approach may help alleviate epileptic symptoms (Hattiangady et al., 2020).

Reducing seizures and improving cognitive and emotional functions

NSC transplantation therapy has been shown to inhibit spontaneous recurrent seizures (SRS) in TLE and alleviate cognitive and emotional dysfunction (Hattiangady et al., 2020). This therapy protects neuropeptide Y-positive and parvalbumin-positive host interneurons, reduces the abnormal migration of newborn neurons, and rescues reelin-positive interneurons in the dentate gyrus (DG). As a result, it maintains higher levels of normal neurogenesis and reduces abnormal mossy fiber sprouting in the DG, significantly inhibiting both the occurrence of epilepsy and the progression of SRS (Hattiangady et al., 2020).

Repairing damaged tissue and enhancing microenvironment

In efforts to replace damaged hippocampal neurons, the effects of various transplantable cells, including fetal hippocampal cell grafts, neuronal precursor cells from the medial

ganglionic eminence (MGE), and other NSCs, have been tested in epilepsy models. A previous study showed that these transplanted cells can promote the neuroprotection and repair of damaged hippocampal tissue (Yasuhara et al., 2013). The transplanted NSCs secrete a variety of neurotrophic factors, such as fibroblast growth factor-2, brain-derived neurotrophic factor, insulin-like growth factor-1, and glial cell-derived neurotrophic factor (GDNF). These factors inhibit inflammation and enhance hippocampal neurogenesis, potentially alleviating the cognitive and emotional dysfunctions caused by epilepsy (Hattiangady et al., 2020). They exert direct and/or indirect effects on neurons by promoting neurogenesis, angiogenesis, synaptogenesis, and exhibiting anti-inflammatory activity (Yasuhara et al., 2013). Additionally, these cells supply growth factors that enhance the survival of neurons in the diseased brain, thus improving the host microenvironment. This, in turn, protects surviving endogenous neurons, which may inhibit the hyperexcitability of abnormal neuronal circuits and replace damaged neurons (Milczarek et al., 2024).

Preclinical trials have been conducted to assess the survival, integration, and functional recovery of transplanted NSCs in drug-induced SE mouse models (**Table 2**). A previous study demonstrated that NSC transplantation reduces SRS by increasing GABAergic activity (Chu et al., 2004). Furthermore, NSC transplantation restores GDNF levels in hippocampal astrocytes, an effect that may underlie the therapeutic effects of MGE-NSC transplantation (Waldau et al., 2010). In models induced by kainic acid, hippocampal NSC transplantation significantly prevented cognitive decline and inhibited the progression of epileptic processes, as well as the frequency and severity of SRS (Hattiangady et al., 2020). Neurosphere transplantation has also shown promise, as its antioxidant system can reduce the oxidative damage caused by epileptic seizures (de Gois da Silva et al., 2018). Further trials are needed to ensure the safety of NSC transplantation. Future work should focus on promoting the long-term survival and integration of neural precursor transplants in the adult brain, optimizing the regulation of neural activity, and developing effective strategies to address concerns related to rejection and tumorigenesis.

Embryonic stem cells

ESCs are derived from the inner cell mass of embryos at the blastocyst stage and are characterized by their significant capacity for self-renewal and their ability to differentiate into all types of somatic cells. Due to their pluripotency, ESCs hold great potential for use in cell replacement therapies for a wide variety of diseases and tissue injuries. The application of ESCs in neuronal regeneration offers significant promise for treating neurological disorders (Deokate et al., 2024). For instance, ESCs derived from rodents have been utilized to generate dopaminergic neurons in mouse models of Parkinson's disease (Rodríguez-Gómez et al., 2007) and to replace photoreceptors to restore vision (Lamba et al., 2009). Furthermore, the transplantation of human ESC-derived neural derivatives into a rat model has been shown to improve functional outcomes after stroke (Hicks et al., 2009). In the context of epilepsy treatment, ESCs can serve three primary functions:

Table 2 | **Preclinical studies of NSCs for epilepsy**

Cell source	Type of transplanted cells	Animal model	Transplant site	Transplant method	Number of cells, frequency and duration of cell administration	Survival of transplanted cells	Effect on seizures	Reference
Ventricular region of embryonic human brain (15th wk of pregnancy)	Human NSCs encoded by β galactosidase	Drug induced SE rats	Undescribed	Tail vein injection	500 μL suspension of HB1.F3 cells (5× cells) for 5 min via a tail vein.	Six wk after transplantation, βgal^{+} cells were found in the hippocampus. While in the striatum, thalamus, and cerebellum, βgal^{+} cells were rarely detected.	Reduced seizures. NSCs differentiate into GABAergic neurons. NSCs transplantation attenuated seizures by increasing GABA activity.	Chu et al., 2004
MGE	MGE-NSCs	KA-chronic SE rats	Hippocampus of rats	Surgical transplantation	Adjust the concentration of surviving cells to a density of 8× cells per microliter. Only using cell suspensions with a survival rate of ≥ 75% for transplantation. Using stereotactic coordinates, inject 6 × 10^{4} live cells from a 0.6 μL cell suspension into the host hippocampus on both sides.	Transplanted cells in the hippocampus (28% of injected) differentiated into NeuN^{+} neurons (13%), S-100β astrocytes (57%), and NG2^{+} progenitor cells (3%). 10% express GABA, and 50% express GDNF.	NSCs transplantation restored GDNF in astrocytes but not neurogenesis. MGE-NSC therapy is effective in TLE, due to the added GABAergic neurons, GDNF^{+} cells, and restoring GDNF.	Waldau et al., 2010
SVZ region of transgenic C57BL/6J mice expressing GFP	NSCs	KA-induced hippocampal degeneration mouse model	Mouse unilateral hippocampus	Anterior hippocampus injection	Animals injected unilaterally with 1 μL GFP-NSCs (1 × 10^{5} cells/μL) from actin-GFP mice in the hippocampus (600 μm rostral to KA site). Injection: 5 min slow, syringe left 5 min, then withdrawn. Skin sutured.	Two animal groups post-KA treatment received cell transplantation: Trip-treated and GFP-NSCs-treated respectively.	Unilateral hippocampal NSCs transplantation prevented KA-induced cognitive decline, protected neurodegeneration, and reduced astrocyte proliferation.	Miltiadous et al., 2013
Wistar rat brain	Neurosphere	Pilocarpine, pentylenetetrazole and Bitter poison model rats	Undescribed	Tail vein injection	0.25 mL, vein injection.	Immunofluorescence confirmed nerve cell presence in 7-d and 15-d cultures.	NSCs therapy showed protective potential, reducing oxidative damage via neural ball's antioxidant system.	de Gois da Silva et al., 2018
Six days after SE and on the 19th day of embryonic development, the hippocampus of the rats was examined	NSCs	Chronic SE rats	Bilateral hippocampus of rats	Stereotactic transplantation	Cells adjusted to 8 × cells/ μL with ≥ 75% viability were treated with BDNF (200 ng/mL) and grafted using stereotaxic coordinates.	Undescribed	Post-SE, hippocampal NSC transplantation inhibited epilepsy progression, SRS frequency/severity, leading to mild chronic epilepsy and better cognitive/emotional functions.	Hattiangady et al., 2020

This table presents a summary of relevant experiments on cell transplantation using NSCs conducted in recent years. It includes basic information, key steps, and results from the literature to facilitate easy searching and analysis. GABA: γ-Aminobutyric acid; GDNF: glial-cell-line-derived neurotrophic factor; GFP: green fluorescent protein; KA: kainic acid; MGE: medial ganglionic eminence; NSCs: neural stem cells; SE: status epilepticus; SVZ: subventricular zone; TLE: temporal lobe epilepsy.

neuron regeneration, the maintenance of cellular homeostasis, and restorative therapeutic activity.

Neuron regeneration

ESCs exhibit a remarkable capacity to differentiate into neural progenitor cells and neurons *in vitro*. When transplanted, these cells can regenerate and integrate into the brain, aiding in the restoration of damaged regions. Studies involving epileptic mice demonstrated the efficacy of transplanting ESC-derived neural progenitor cells (ESNPs) into the cornu ammonis-3 region of the hippocampus and the hippocampal fimbria (Carpentino et al., 2008; Liu et al., 2018; Rodriguez-Jimenez et al., 2021). These transplanted ESNPs migrated to the DG and functioned similarly to NSCs (Martin et al., 1999), with some differentiating into DG neurons. Additionally, ESNPs transplanted into the fimbria exhibited the ability to extensively migrate along pre-existing fiber bundles, ultimately differentiating into oligodendrocytes or astrocytes. This research indicates the benefits of exploring factors and conditions that enhance the generation and transplantation of ESCs (Rodriguez-Jimenez et al., 2021), which could pave the way for novel therapeutic strategies for neurological restoration, including those that alleviate the symptoms experienced by patients with epilepsy (Zayed et al., 2022).

Cellular homeostasis

Stem cells play a crucial role in maintaining the cellular balance throughout various neurological processes (Liu et al., 2022). Due to their robust modulatory properties, ESCs contribute to cellular homeostasis by releasing a variety of cytokines (Pahl et al., 2021; Goldberg et al., 2024). Their ability to stabilize damaged tissues and cellular environments is pivotal in preventing the onset and progression of epilepsy. As a homeostatic bioenergetic network regulator, adenosine is well-suited to establishing or restoring the ongoing balance between excitation and inhibition, and its anticonvulsant efficacy is well established (Masino et al., 2014). Gene-edited human ESC-derived neuroepithelial stem cells (Koch et al., 2009; Falk et al., 2012), in which the adenosine-metabolizing enzyme ADK gene was knocked out, exhibited significantly elevated adenosine release, as did the neurons and astrocytes resulting from their differentiation (Poppe et al., 2018). Furthermore, the differentiation of ESCs triggered a more extensive release of adenosine, indicating ESCs' potential activity-dependent regulatory role while simultaneously demonstrating their powerful immunoregulatory effects during the differentiation process.

Substitutive therapy

ESCs can differentiate into functional neurons that can be transplanted into the brains of epilepsy rats to replace damaged or abnormally discharging neurons (Liu et al., 2013). For example, intermediate progenitor cells derived from human ESCs can be used to generate MGE precursor cells. These precursor cells can then be further induced to differentiate into pallial interneurons (Maroof et al., 2013), which are specialized neurons capable of inhibiting abnormal brain activity through the release of GABA and thereby effectively reducing the frequency of seizures (Maroof et al., 2013) (**Figure 4**). Research on ESC transplantation for the treatment of epilepsy has gained significant attention in recent years, and relevant studies are listed in **Table 3**.

Transplantation of medial ganglionic eminence progenitor cells

TLE often causes hippocampal damage in patients, leading to SRS, as well as cognitive and emotional dysfunction. AEDs typically only terminate SE, rather than inhibit the occurrence of epilepsy and the progression of TLE (Zayed et al., 2022). A key pathological hallmark of TLE is a loss of GABAergic interneurons. GABA is released into synapses following the formation of axonal terminals by inhibitory neurons, where it interacts with GABAA or GABAB receptors (Welle and Smith, 2024). The GABAA receptor mediates its effects by regulating the influx and efflux of chloride ions (Cl^-) across cell membranes, thereby influencing the initial phase of GABA-mediated inhibitory postsynaptic potentials (IPSPs). In contrast, the GABAB receptor enhances potassium (K^+) conductance, inhibits calcium (Ca^{2+}) conductance, and suppresses the presynaptic release of other neurotransmitters, thus impacting the later phase of IPSPs (Sperk et al., 2004). GABA is swiftly removed from the synaptic cleft by its uptake into glial cells and presynaptic nerve endings, where it is subsequently metabolized by transaminase enzymes. Prior research has demonstrated a loss of specific GABAergic neuron populations within the hippocampus in animal models of epilepsy and in temporal lobe tissues from patients with DRE, particularly from the CA1 and CA3 regions. However, granule cells in the DG and pyramidal neurons in the CA2 region exhibit a less sizable loss (Sloviter, 1994). Electrophysiological and neurochemical studies indicate that GABA at the synapse can increase in transmission to compensate. Furthermore, receptor loss due to neurodegeneration is accompanied by significant alterations in the expression of receptor subunits in other areas of the DG and hippocampus. These changes may be closely associated with the recurrence of DRE, the enhancement of endogenous protective mechanisms, and the development of resistance to AEDs.

Transplanting interneurons derived from the MGE can enhance the proportion of inhibitory neurons within the epileptic focus, thereby inhibiting SRS (Williams and Riedemann, 2021). Human MGE (hMGE) cells are well-suited for the treatment of TLE, as they differentiate into mature GABAergic interneurons upon transplantation. In a mouse model of TLE induced by pilocarpine, the bilateral hippocampal transplantation of MGE progenitor cells resulted in a significant reduction in the frequency of spontaneous epileptic seizures (Hunt et al., 2013). The transplanted cells also expressed markers of inhibitory neurons, including parvalbumin, somatostatin, and neuronal nitric oxide synthase, in the hippocampal region. Similar results have been observed in rats with chronic epilepsy, i.e., a decrease in the frequency and intensity of SRS as well as the total seizure duration (Shetty and Upadhya, 2016), further validating the therapeutic efficacy of this treatment.

Electrophysiological assessments have confirmed that GABA-mediated inhibitory function is enhanced post-transplantation, with an increase in spontaneous and miniature inhibitory postsynaptic currents (IPSCs) (Allison et al., 2021). However, the transplantation of cells from the caudal ganglionic eminence did not improve seizure conditions in mice. Over time, the functionality of the transplanted cells matured, with a significant increase in sodium and potassium currents observed 6 months post-transplantation (Li et al.,

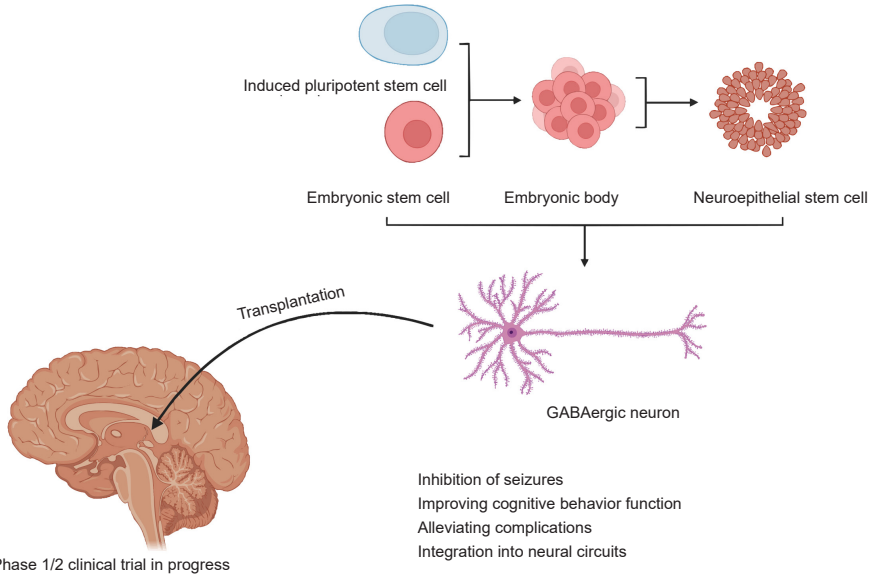

Figure 4 | **The process of differentiation of embryonic and induced pluripotent stem cells for epilepsy.**
This image illustrates the process by which embryonic stem cells and induced pluripotent stem cells differentiate into neurons for the treatment of epilepsy. Initially, these stem cells aggregate to form embryoid bodies. They then differentiate into neuroepithelial stem cells with a rosette structure through induction and ultimately develop into GABAergic neurons, which play an antiepileptic role when transplanted into the hippocampus. In preclinical studies, these cells have demonstrated significant antiepileptic effects following hippocampal transplantation (Bershteyn et al., 2023; Zhu et al., 2023). This innovative treatment approach has shown promising results and has now advanced to clinical Phase 1/2 trials. Created with BioRender.com. GABA: γ-Aminobutyric acid.

Table 3 | **Preclinical studies of ESCs for epilepsy**

Type of transplanted cells	Animal model	Transplant site	Survival of transplanted cells	Host loop and nerve changes	Effect on epileptic seizures	Long-term effect	Reference
GABA-ergic interneurons	PILO-TLE+KA-TLE mice model	Hippocampus of mice	After 4 mon of transplantation, only 0.07% cells remained in GABAergic interneurons. At 10 mon after transplantation, the transplanted interneurons had shown neuron function in the host circuit.	The decrease of inhibitory synapses in dentate gyrus increased, and most of the innervation of interneurons came from hippocampus, which integrated into the host loop to release GABA.	Significantly reduced the frequency of seizures and relieved anxiety symptoms.	At 9 mon after transplantation, the frequency of epileptic seizures was reduced, and complications were improved.	Zhu et al., 2023
GABA cINs	KA-induced chronic epilepsy model mice	CA3 region of hippocampus in mice	The transplanted MGE-cINs can form functional synapses in dentate gyrus of epileptic mice for a long time (1.5 yr).	Synaptic connections were formed in the hippocampus, and SEPSC mediated by glutamate was received, integrating into the globus pallidus and reducing the dispersion of dentate granule cells.	Significantly reduced seizure frequency and duration, along with improved learning, memory, and survival rates.	7 mon after transplantation, frequency of seizures decreased and the duration of seizure shortened.	Bershteyn et al., 2023
MGE	KA-induced SRS model rats	Hippocampus of rats	All cINs expressed the DREADDs receptor derived from ESCs, confirming that the transplanted MGE progenitor cells developed into functional neurons.	Graft-derived neurons form synaptic connections with rat CA1 pyramidal neurons and dentate granule cells.	Reduced seizure frequency and duration; enhanced cognition, memory, and pattern separation.	Undescribed	Upadhya et al., 2022
GABA cINs	KA-induced SE model rats	Hippocampus of rats	At 3 and 6 mon post-transplantation, the transplanted neurons emitted depolarization-induced action potentials, indicating that the function of GABA cINs matures over time.	Derived GABA cINs form synapses with rat neurons.	Reduced rate of epileptic discharge ex vivo and the frequency of epileptic seizures in rats.	Undescribed	Waloschková et al., 2021

This table summarizes the essential details, key procedures, and long-term results of recent research on the transplantation of ESCs that have undergone directed differentiation into cells suitable for epilepsy models, providing a concise overview for further analysis. CA: Cornu ammonis; cINs: cotransmitting intermediate neurons; DREADDs: designer receptor exclusively activated by designer drugs; ESCs: embryonic stem cells; GABA: γ-aminobutyric acid; KA: kainic acid; MGE: medial ganglionic eminence; PILO: pilocarpine; SE: status epilepticus; SEPSC: spontaneous excitatory postsynaptic current; SRS: spontaneous recurrent seizures; TLE: temporal lobe epilepsy.

2022). Additionally, hESC-derived interneurons formed inhibitory synapses with host neurons and reduced the rate of epileptiform discharges ex vivo, as well as the seizure frequency in rats (Waloschková et al., 2021).

Future research could explore the functions of different neural circuits formed post-transplantation. One promising approach involves using designer receptors exclusively activated by designer drugs (DREADDs) (Botterill et al., 2021; Panthi et al., 2021) through chemogenetic methods to express a synthesized G-protein-coupled receptorgene hM4di in neurons (Chen et al., 2016). This receptor opens potassium channels, allowing potassium ions to flow into the cell and inhibit neuronal activity (Botterill et al., 2019). Goossens et al. (2021) successfully generated hESCs expressing a stable inhibitory DREADD using CRISPR/Cas9 technology. These cells were able to differentiate into hMGE progenitor cells that produce GABAergic interneurons. Using clozapine-N-oxide (CNO), Desloovere et al. (2022) silenced these interneurons. Activating DREADD with CNO led to an increase in the number of SRS, as well as increased seizure intensity and duration; however, after the CNO washout period, seizure levels returned to their previous lowered state (Upadhya et al., 2022).

TLE often results in volume reduction and sclerosis of the hippocampus, disrupting hippocampal circuits and impacting cognitive functions. Transplanting hMGE cells into the hippocampus alleviated chronic epilepsy-induced impairments in object location memory, which is hippocampus-dependent (Anderson et al., 2018). The GABAergic interneurons derived from these transplanted hMGE cells contributed to this improvement in memory function. Additionally, pattern separation—a primary function of the DG region of the hippocampus (Hattiangady et al., 2014)—involves the ability of the brain to form distinct memories from highly similar yet slightly different events or stimuli. This cognitive process is often among the first to be affected in various central nervous system disorders, including aging, Alzheimer's disease, and chronic epilepsy (Leutgeb et al., 2007; Yassa and Stark, 2011). The transplantation of hMGE cells has also been found to improve pattern separation function in epileptic animals. However, in contrast to their direct impact on object location memory, GABAergic interneurons do not directly influence pattern separation (Upadhya et al., 2022).

Following the transplantation of hMGE cells, structural evaluations revealed that more than 80% of the surviving transplanted cells differentiated into GABAergic interneurons. These neurons formed synaptic connections with both CA1 pyramidal neurons and dentate granule cells in the hippocampus (Upadhya et al., 2022). This integration led to the long-term suppression of hyperactivity in dentate granule cells (Goossens et al., 2021) and the simultaneous enhancement of endogenous neurogenesis in the hippocampus (Upadhya et al., 2019b). These observations align with this strategy's effective control of epileptic seizures and enhancement of object location memory function.

Transplantation of gamma-aminobutyric acidergic interneurons

As researchers gain a deeper understanding of the differentiation process of ESCs, remarkable advancements are being made in their ability to harness these cells for therapeutic applications. Leung et al. (2015) transplanted GABA-cotransmitting intermediate neurons (cINs) derived from H9 ESCs into the hippocampus of mice with TLE. At 4 months post-transplantation, these cells had migrated extensively within the hippocampus and expressed markers characteristic of cIN subtypes, such as calcium-binding protein, somatostatin, and parvalbumin (Nicholas et al., 2013; Rho and Boison, 2022). This indicated that the transplanted cINs had matured into appropriate phenotypes *in vivo* and integrated into the host neuronal network (Ni et al., 2019). Video electroencephalography analyses conducted to assess the efficacy of cIN transplantation revealed a significant reduction in seizure frequency and duration in the transplant group. Even 9 months after cIN transplantation, sustained seizure suppression was observed, with no significant change in the total number of surviving cells in the transplant region. Importantly, histological results of the grafts examined 9 months post-transplantation revealed that the majority of cells expressed SOX6, with no detectable expression of Ki67, even after an extended period of proliferation *in vivo*. This confirmed the safety of the chemically matured human cIN grafts in mice (Zhang et al., 2012). Furthermore, stereological analysis demonstrated a significant increase in the total graft volume at 9 months, suggesting ongoing cell migration occurred within this timeframe (Gupta and Naegele, 2023b). Notably, no apoptotic grafted or host neurons were observed 1 week or 4 months post-transplant, as evidenced by the lack of expression of the apoptotic marker cleaved caspase-3. However, it should be noted that necrosis of host neurons in the needle tract due to mechanical trauma is a possibility in the acute phase immediately after grafting (Zhu et al., 2023). The evidence suggests that cIN transplantation can restore the lost inhibitory-excitatory balance in the hippocampus of TLE mice (Hainmueller and Bartos, 2020), providing a mechanistic basis for the attenuation of seizures.

In addition to its efficacy in reducing seizures, cIN transplantation has also shown potential in alleviating the comorbidity symptoms associated with TLE, such as anxiety, depression, social deficits, and cognitive impairments (Rini and Ochoa, 2020). Tests conducted 6 months post-transplantation indicated there was an increase in presynaptic inhibitory input in dentate granule cells, without any change in amplitude, confirming the safety of the procedure. Furthermore, the transplanted cINs alleviated the anxiety symptoms of epileptic mice placed in the Elevated Plus Maze, potentially functioning similarly to the anxiolytic effects of GABA receptor agonists (Alhashimi et al., 2022). In the sucrose preference test, the researchers observed that cIN transplantation restored the sucrose preference of TLE mice. Additionally, in social interaction tests, the Y-maze test, and the novel object recognition task, the results indicated that cIN transplantation was able to reverse the negative impact of epilepsy (Zhu et al., 2023). While GABA receptor agonists administered at high doses can lead to various adverse side effects, such as sedation, drowsiness, and motor weakness due to the over-inhibition of neural circuitry, researchers investigated this by analyzing spontaneous IPSCs (sIPSCs) in host granule cells 6 months after transplantation. They found that, compared to naïve mouse controls, the group that received human cIN grafts had a significantly higher frequency of sIPSCs in the host granule cells, while the amplitude of sIPSCs remained unchanged. This suggests these neurons received increased presynaptic inhibitory inputs (Zhu et al., 2023), an observation that hints at the existence of an auto-regulatory mechanism that limits the overall level of inhibition as the density of grafted cINs increases. These findings further support the *in vivo* safety of human cIN grafts, indicating that they are unlikely to cause over-inhibitory side effects in the grafted subjects (Gupta and Naegele, 2023a).

Structurally, the transplanted cINs became integrated into the host's neuronal circuitry in a manner similar to developmental integration. Transplanted cINs in the DG region exhibited an increase in inhibitory neurons and a decrease in excitatory neurons (Zhang et al., 2012). Most of the neuronal innervation of the graft originated from within the hippocampus, including the hilus, CA1, and CA3 regions (Piao et al., 2021), with a smaller contribution from the cortex, amygdala, and septum. This suggests that transplanted cINs can integrate into the host's neural circuits within the epileptic environment and release GABA to counteract excessive excitation (Zhu et al., 2023).

To characterize the differentiation process more objectively, Pai et al. (2020) used single-cell RNA sequencing and magnetic purification for the positive selection of differentiated cINs. These techniques revealed that MGE-derived pINs from hESCs were morphologically and migratorily similar to fetal MGE-derived pINs, thus confirming their functional specificity during migration and enhancing the efficiency and reproducibility of subsequent experiments. Transplanting purified cINs into the brains of epileptic mice resulted in more pronounced effects, with a dose-dependent relationship observed between the number of transplanted cINs and seizure suppression (Waloschková et al., 2021; Bershteyn et al., 2023). This purified transplant also improved common comorbidities associated with refractory epilepsy (Pereira Dalio et al., 2022), such as learning and memory impairments (Chaunsali et al., 2021).

The dose of transplanted cells is a critical factor in determining the success of the treatment. Research demonstrated that there is an optimal dose range within which cell transplantation can markedly reduce the frequency and duration of epileptic seizures. Specifically, at lower doses, such as 25,000 cells per hippocampus, the inhibitory effect on epilepsy was not pronounced. As the dose increased to 50,000 cells per hippocampus, an inhibitory effect began to emerge, albeit to a limited extent. However, when the dose was further increased to 200,000 cells per hippocampus or higher, cell transplantation exhibited a significant inhibitory effect on epilepsy. At the highest dose, when 1.5 million cells per hippocampus were transplanted, most animals experienced a complete cessation of epileptic seizures for an extended period post-transplantation. This indicated there was a positive correlation between the dose of hMGE-pINs transplanted and their inhibitory effect on epilepsy within a specific dose range (Zhu et al., 2023).

It is important to note that, while the high-dose group demonstrated the most pronounced inhibitory effect on epilepsy, there was a significant decline in the survival rate of cells in the host hippocampus as the dose increased. Specifically, at a dose of 1.5 million cells per hippocampus, the long-term survival rate of the initial cells fell below 2%. This finding suggests the existence of a maximum tolerable cell density threshold, beyond which cell survival is compromised due to factors such as insufficient nutrient supply, spatial limitations, or immune responses in the host environment. Consequently, when determining the optimal dose for transplantation, it is crucial to balance the therapeutic benefits against the potential impact on cell survival rates (Zhou et al., 2024b).

Another study investigated whether the high-density transplantation of cINs could lead to excessive inhibition within neural circuits. Utilizing three-dimensional imaging analysis, researchers assessed the density of transplanted human cINs and examined the correlation between transplantation density and the level of inhibition in host neurons. The findings revealed that, although transplantation resulted in a significant increase in the frequency of sIPSCs, this increase plateaued at relatively low transplantation densities. Furthermore, as transplantation density increased, additional increments in inhibition were minimal. This suggests the presence of an intrinsic regulatory mechanism limits the overall increase in inhibition as the density of transplanted cINs rises (Bershteyn et al., 2023).

From a practical application perspective, determining the optimal transplantation dose is crucial for the success of cell transplantation therapy. Excessively high doses may lead to decreased cell survival rates, while excessively low doses may fail to achieve the desired inhibitory effect on epilepsy (Chen et al., 2024a). Therefore, future research must further experiment with the dose of transplanted cells to identify the optimal balance point that effectively inhibits epileptic seizures while ensuring high cell survival rates. The transplantation of human cINs is unlikely to cause excessive inhibition in transplanted subjects, supporting its safety for *in vivo* use. Additionally, the observed automatic regulatory mechanism may be significant for understanding the integration and functional regulation of transplanted neurons within the host brain. By conducting in-depth research on changes in cell survival rates, migration patterns, differentiation states, and integration with host neurons at different doses, we can gain a better understanding of the mechanisms underlying cell transplantation therapy and provide a solid scientific basis for its clinical application in epilepsy treatment.

Given the broad therapeutic range and lack of adverse reactions observed in preclinical studies, the research team extended this approach to clinical applications (Shin et al., 2022; Humayun et al., 2024). A phase 1/2 clinical trial for refractory unilateral mesial TLE (NCT05135091) is currently underway (Xu et al., 2024). The trial aims to test a method of controlling seizures by repairing and remodeling neural networks in the brain while evaluating the safety and preliminary efficacy of cellular therapy. This study was designed as an open-label, multicenter clinical trial, with plans to recruit approximately 40 patients. Participants will receive a single stereotactic intracranial administration of GABA-secreting interneurons (Chen et al., 2024a), followed by a 2-year postoperative follow-up assessment. The primary endpoint is safety, assessed 1 year post-implantation, with seizure frequency as a secondary endpoint. Additional endpoints include assessments of EEG, neuroimaging, cognitive performance, and visual fields (Babu et al., 2024). Preliminary data collection is ongoing, and the participants' recovery, along with changes in seizure activity, is being closely monitored to ensure the safety and efficacy of the treatment. If the clinical study shows favorable safety and preliminary efficacy results, it could offer a new therapeutic option for patients with refractory unilateral mesial TLE (Zhou et al., 2024b) and potentially advance the application of stem cell transplantation in the field of epilepsy (Chen et al., 2024b).

As of October 2023, five patients have been enrolled in the NRTX-1001 treatment study, with follow-up periods ranging from 1 to 15 months post-treatment (MPT). To date, no serious adverse events have been reported. Notably, Subject #1, who is at 15 MPT, has achieved a greater than 90% reduction in seizures and has been free of awareness-impaired seizures since 1 MPT. Similarly, Subject #2, who is at 11 MPT, has also experienced a more than 90% reduction in seizures, along with a greater than 50% decrease in awareness-impaired seizures. Additionally, both subjects have shown quantitative improvements in specific memory function assessments (Babu et al., 2024).

In the low-dose group of the NRTX-1001 study, patients experienced a median reduction of 92% in disabling seizures compared to baseline during the primary efficacy evaluation, which occurred 7–12 MPT. Approximately 80% of patients in this group

reported a seizure reduction of over 75%. Notably, the first two patients treated with low-dose cell therapy continued to report seizure reductions exceeding 97% 2 years after a single treatment. In the high-dose group, the median number of disabling seizures decreased by 78% compared to baseline during the mid-term evaluation conducted 4–6 MPT, and 60% of patients reported a seizure reduction of more than 75%. NRTX-1001 transplantation has been safely administered to five patients with drug-resistant TLE. The preliminary results, available for two subjects at approximately 1 year post-treatment, indicated that NRTX-1001 transplantation may enhance seizure control and alleviate memory dysfunction. Thus far, both high-dose and low-dose NRTX-1001 has demonstrated good tolerability. In contrast to current surgical treatments (e.g., resection and laser ablation), NRTX-1001 could provide a non-destructive and functionally restorative approach to treating focal epilepsy (Babu et al., 2024).

Induced pluripotent stem cells

iPSCs are reprogrammed somatic cells from fibroblasts or vascular tissues that possess the remarkable ability to convert to a pluripotent state by overexpressing specific genes. These cells share the same genetic background as the donor, significantly reducing the risk of immune rejection and alleviating ethical concerns. By capturing the genetic characteristics of any disease a patient may have, human iPSCs can illustrate the various stages of the disease and simulate the individual or cumulative effects of defective genes (McTague et al., 2021). This makes them invaluable for understanding complex diseases with both genetic and sporadic origins.

Disease modeling

iPSCs can be utilized to create patient-specific neurons that simulate epileptiform hyperactivity, providing an excellent platform for understanding disease mechanisms (Danačíková et al., 2024). By combining stem cell induction methods with gene editing tools such as CRISPR/Cas9 or TALEN, Danačíková et al. (2024) generated isogenic controls by correcting specific mutations while preserving the patient's unique genetic background. These iPSC lines can be differentiated into specific cell types to model various aspects of disease mechanisms (Heinrich et al., 2010). For example, introducing the point mutation A5768G into the *SCN1A* gene, which encodes the Nav1.1α subunit of the voltage-gated sodium channel, allows for the creation of iPSC lines that maintain their pluripotency and differentiate into neurons with normal functional characteristics (Heinrich et al., 2010). The only difference between these cell lines lies in their susceptibility to epileptic variants, making them valuable for generating human cellular models (Torper et al., 2013).

Neurons derived from human iPSCs can be analyzed in two-dimensional systems or cultured into three-dimensional organoids for in vitro injury simulations. These organoids can be molecularly modified and subsequently used for real-time imaging and electrophysiological experiments involving optical stimulation. By integrating human 3D organoids with modern optogenetics, chemogenetics, and imaging tools, researchers can gain new insights into injury mechanisms (Hirose et al., 2020). Brain-like organoids have a more physiological three-dimensional structure that allows for the study of the entire brain and can generate various cell types related to human brain diseases (Danačíková et al., 2024).

High-throughput drug screening

iPSC-derived neurons from epileptic patients can be used to uncover new insights into how specific gene mutations affect neuronal excitability, migration, dendritic or axonal differentiation, and synaptogenesis at the cellular level. They also help in elucidating the neuropathophysiology of neurons and their responses to drug treatments, making them effective tools for screening AEDs. Based on their cellular responses to various drug compounds, more effective medications can be selected and administered to individual patients (Li and Chen, 2016). A recently developed platform, the porous multi-electrode array platform, offers a unique opportunity for epilepsy research by enabling the rapid screening of large drug libraries on patient-derived neurons (Zhao et al., 2024).

Cell transplantation therapy

iPSC technology has revolutionized the field of regenerative medicine, offering the potential for the design of personalized cellular therapies. Human iPSCs can differentiate into long-term self-renewing neuroepithelial stem cells (NES), primarily forming GABAergic neurons. The transplanted cells exhibit unique electrophysiological characteristics, indicating a prolonged process of differentiation, maturation, and synaptogenesis has occurred (Lu et al., 2023). iPSC transplantation may help increase the release of inhibitory neurotransmitters and normalize hyperexcited neuronal networks in epilepsy (Chang and Chang, 2022). The implantation of human iPSC-derived MGE-like intermediate neuronal precursors into the hippocampus of epileptic rodents demonstrated antiepileptic and anticonvulsant effects, significantly inhibiting the epileptic phenotype and reducing cell loss, abnormal neurogenesis, and abnormal mossy fiber sprouting (Srivastava and DeWitt, 2016).

Currently, research on iPSC cell therapy is in the preclinical experimental stage. Research is being conducted on the transplantation of personalized neurons derived from iPSCs into Xenopus laevis oocytes via membrane injection (Limongi et al., 2022). A study on the intranasal delivery of extracellular vesicles (EVs) derived from GABA-producing cells and their progenitor cells demonstrated that exogenous GABA can be transmitted to the brain via these EVs, thereby regulating the onset of TLE (R et al., 2024). Additionally, research on targeted drug delivery through viral vectors has shown promising results. The human long-term self-renewing neuroepithelial stem cells (hL-NES) produced by human iPSCs were reported to differentiate into neurons *in vitro* and receive functional synaptic inputs after transplantation into the rat hippocampus in vivo; they ultimately exhibited antiepileptic effects and improved cognitive and emotional functions (Upadhya and Shetty, 2019). More detailed information is provided in **Table 4**.

To facilitate the identification and isolation of viable GABAergic neurons from iPSC lines, a cell type–specific promoter-driven fluorescent reporter gene construct has been developed. This construct utilizes the human vesicular GABA transporter (hVGAT) promoter to specifically drive the expression of mCherry in VGAT-expressing neurons. Transducing iPSC-derived forebrain neuronal cultures with an hVGAT promoter-mCherry lentiviral reporter gene vector generated specifically labeled GABAergic neurons (Rao et al., 2021b). Cell-based therapies for DRE using iPSC-derived inhibitory interneurons are now in early-phase clinical trials (Beaudreault et al., 2024), and iPSC transplantation has proven to be safe and effective in reducing seizures in rodents. This non-pharmacological approach holds promise for providing long-term or permanent management of epileptic seizures.

Before clinical application, rigorous genetic screening is essential to ensure the safety of transplanted cells. To mitigate potential risks, numerous advanced genetic methods have been developed, including single virus cassettes, non-integrating adenoviral vectors, synthetic mRNA, transient plasmid transfection, transposons, Cre-excisable vectors, and oriP/EBNA1-based episomal expression systems (Matsuda et al., 2019). Additionally, the high cost of personalized cell transplantation therapy poses challenges for many patients (Sunwoong et al., 2024). Research focused on identifying cell lines compatible with human leukocyte antigen (HLA) genes suggests that developing representative HLA haplotype cell lines for each region could lead to more effective cell therapies, offering improved strategies for iPSC therapy (Sunwoong et al., 2024). Furthermore, by acknowledging that most diseases are influenced by environmental risk factors, iPSC-based models can be enhanced by incorporating relevant physical and chemical stimuli (Guo et al., 2014). These models enable the precise control and detailed investigation of the interplays between genetic and environmental factors, thereby providing a more comprehensive understanding of disease mechanisms and potential therapeutic interventions.

Organoid application

Organoids are three-dimensional biological structures grown in the laboratory from stem cells or specific cell types and can mimic the structure and function of human tissues (Eichmüller et al., 2022). Organoids exhibit electrophysiological activities similar to those of the brain and can be modified at the molecular level, allowing for real-time imaging and experimentation using modern techniques such as optogenetics, chemogenetics, and various imaging tools. In epilepsy research, iPSCs or hESCs can be utilized to create organoids that replicate the early development of the human brain (Gross, 2022). These brain organoids are particularly useful for studying epilepsy, as they provide more accurate models of disease states.

Moreover, various organoids are valuable for drug screening research. By testing anti-seizure medications on organoids derived from epilepsy patients, researchers can precisely evaluate their therapeutic efficacy and potential side effects. This approach also helps identify new drug targets and understand the mechanisms of drug resistance. For instance, in patients with CDKL5 deficiency disorder, electrophysiological recordings of their cortical organoids revealed higher densities of sodium (Na) and potassium (K) currents, as well as a negative shift in Na channel activation (Wu et al., 2022), providing potential new drug targets for the early treatment of this disorder.

Table 4 | **Preclinical studies of iPSC for epilepsy**

Source of iPSC	Type of transplanted cells	Animal model	Transplant site	Transplant method	Specify the number of cells, frequency and duration of cell administration	Survival of transplanted cells	Effect on seizures	Reference
Skin fibroblasts from Italian patients with specific genetic characteristics carry the c.434T>C mutation in the *SCN1A* gene.	Neuron	Xenopus oocytes	Undescribed	Membrane injection	Undescribed	Neuroepithelial stem cell	Mutant NaV1.1 neurons were utilized to aid personalized epilepsy treatment and drug screening.	Scalise et al., 2022
Reprogramming of fibroblasts in healthy male newborns	NSCs-MGE and GABA-cIN	KA-induced SE in Fisher rats	Undescribed	EV intranasal transport of GABA- producing cells and their progenitor cells	Epileptic rats (n = 8) were intranasally treated with IN-EV-GABA daily for 7 d at both 4 and 5 mon, and with NSC-EV-GABA daily for 7 d at 6 mon. Rats were anesthetized and received 30 µL GABA-loaded EVs intranasally per nostril in 10 µL spurts, avoiding mucous membrane damage.	Undescribed	Exogenous GABA transmitted via brain cell-derived EVs regulates TLE seizures. EV cell source was crucial for seizure control.	Ballal et al., 2024
hiPSC	Neuroepithelial stem cells mainly form GABAergic neurons.	*In vitro* model of overexcited epileptic tissue (i.e. OHSCs) and in rats	Hippocampus	Stereotactic injection of virus vector	Cells were resuspended in DMEM/F-12 at 5×10^6 cells/mL for hippocampal slice application (cells/slice) and in cytocon buffer at cells/µL for intrahippocampal injection (3 µL total per hippocampus, 1 µL at each D-V coordinate), 1-wk post-AAV injection for virus clearance.	At all time points, transplanted cells are observed in OHSC, mainly in the main cell layer. Over time, the transplanted cells developed into neuron-like shapes with finer dendritic structures.	Neuroepithelial stem cells from human iPSC differentiated into neurons with synaptic input post-transplantation. Host-derived connections regulated GABA release to normalizing brain networks.	Avaliani et al., 2014
hiPSC	MGE-like intermediate neuron precursor	KA-induced SE in rats	Hippocampus	Injection of hMGE cell graft transduced by AAV5 vector carrying HSYN-HM4DI M Cherry Dream DS	Neurospheres were dissociated and induced with sonic hedgehog for 24 h. They were then transduced with AAV5-hSyn-hM4Di-mCherry for 48 h and subsequently washed by centrifugation to achieve over 85% viable cells. A 1 µL suspension of subventricular zone neural stem cells containing 1×10^6 live cells was injected into three sites in the hippocampus, delivering a total of 3×10^5 cells per hippocampus in spurts over 1 to 2 min.	Graft-derived cells survived, migrated widely in the hippocampus, and differentiated into inhibitory interneurons expressing calcium-binding proteins and neuropeptides.	Following status epilepticus, the transplantation of MGE hiPSC-derived cells into the hippocampus resulted in a reduction of spontaneous seizures. This intervention also led to decreased neuron loss, abnormal neurogenesis, and mossy fiber sprouting. Additionally, improvements in cognitive and emotional functions were observed.	Upadhya et al., 2019a

This table presents relevant experiments on cell transplantation using iPSCs conducted in recent years. It summarizes essential information, key steps, and results of transplantation as reported in the literature, facilitating easier search and analysis. AAV: Adeno-associated virus; EV: extracellular vesicle; GABA: γ-aminobutyric acid; hiPSCs: human induced pluripotent stem cells; hMGE: human medial ganglionic eminence; iPSCs: induced pluripotent stem cells; KA: kainic acid; MGE: medial ganglionic eminence; NSCs: neural stem cells; OHSCs: organotypic hippocampal slice culture; TLE: temporal lobe epilepsy.

Organoid transplantation offers a promising approach for reconstructing damaged neural tissue and restoring its function (Lancaster et al., 2013). This technique is particularly useful for diseases such as stroke, schizophrenia, and autism. For example, researchers from Nanjing Medical University successfully transplanted human brain organoids into a stroke mouse model and demonstrated that the transplanted organoids could repair infarcted tissue, restore impaired functions, and eliminate sensory-motor deficits (Cao et al., 2023). These findings underscore the immense potential of organoid transplantation for treating brain disorders and offer new hope for patient recovery.

Despite the significant potential of organoid technology use in epilepsy research, several challenges must be addressed. One major limitation is that organoids are not as mature or functional as *in situ* brain tissue. Future studies should focus on enhancing their developmental levels and functional characteristics. Additionally, organoids lack complex *in vivo* microenvironments, including the blood–brain barrier and interactions with neural support cells, which could affect the accuracy of experimental results (Sandoval et al., 2024).

To overcome these challenges, researchers will likely need to explore various strategies, such as microfluidics and 3D printing, to construct more sophisticated organoid models (Wang et al., 2023). Another important consideration is the ethical issues surrounding the use of organoids derived from human cells, particularly regarding patient privacy and the transparency of cell sources (Faltus et al., 2023). By continuing to investigate the application of organoids in epilepsy, we can gain a better understanding of disease mechanisms, facilitate the development of new drugs, and ultimately improve the quality of life of patients.

Astrocyte Transdifferentiated Into Neurons

Astrocytes, which account for approximately 30% of neuroglia, are widely distributed throughout the central nervous system and represent the most abundant cell type in the adult mammalian brain (Liddelow and Barres, 2017). A previous study demonstrated that astrocytes possess a remarkable ability to transform into functional neurons (AtN transformation) (Heinrich et al., 2010). Unlike non-dividing neurons, astrocytes can proliferate, making them an ideal source for cell transformation (Wu et al., 2020b). Utilizing

in situ astrocytes for neural regeneration has the advantage of minimizing immune rejection (Li and Chen, 2016).

Various methods have been developed to reprogram reactive glial cells into functional neurons *in vivo*, as shown in **Table 5**. These methods include the ectopic expression of neural transcription factors (Matsuda et al., 2019), knockout of specific genes (Qian et al., 2020), overexpression of a single transcription factor such as NeuroD1 (Guo et al., 2014), use of an engineered adeno-associated virus (AAV) Cre-FLEX system (Chen et al., 2020), and application of small-molecule compounds (Zhang et al., 2015). Rao et al. (2021b) demonstrated that NeuroD4 and Chd7 are essential for efficient AtN transformation induced by Ascl1, regulating the generation of interneuron protrusions primarily through the early expression of Klf10. Further research showed that using the CRISPR-CasRx system *in vivo* to downregulate polypyrimidine tract-binding protein 1 (Ptbp1) can facilitate the conversion of glial cells into different types of neurons in various brain regions (Zhou et al., 2020). Additionally, a study by Wu et al. (2020b) demonstrated that, in the R6/2 and YAC128 Huntington's disease mouse models, astrocytes in the mouse striatum could be reprogrammed to differentiate into GABAergic neurons through the rAAV2/5-mediated co-expression of NeuroD1 and Dlx2, resulting in reduced atrophy and improved motor function in HD mice.

However, the widespread use of lineage-tracing technology has led some researchers to question the methodology used for transforming astrocytes into functional neurons. Lineage-tracing studies in the mouse brain have revealed that the functional neurons induced by NeuroD1 predominantly originated from AAV-infected endogenous neurons rather than from astrocytes, as previously thought (Wang et al., 2021). Additionally, attempts to knock down Ptbp1 have failed to achieve AtN transformation (Chen et al., 2022), possibly due to viral leakage. Another study confirmed the occurrence of lentiviral leakage during the transformation process, finding that NeuroD1 induced microglial apoptosis but did not reprogram them into neurons (Rao et al., 2021a). Efforts to reduce the AAV dose or modify the AAV serotype and injection route have proven ineffective in preventing leaky expression (Xie et al., 2023). Prof. Chen addressed the concerns regarding "viral leakage," suggesting that the results may stem from the high doses of AAV used in Dr. Zhang's laboratory (Wang et al., 2021; He et al., 2025). They further provided direct visual evidence for the AtN conversion process through techniques such as lineage tracing and two-photon live imaging (Xiang et al., 2021, 2024).

Despite the existing controversies, astrocyte reprogramming technology holds significant potential for the treatment of epilepsy (**Figure 5**). A decrease in inhibitory GABAergic interneurons contributes to the development of TLE. Consequently, generating GABAergic interneurons through *in vivo* cell conversion has emerged as a promising therapeutic approach for TLE. In a mouse model of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), the retroviral-driven transcription factors Ascl1 and Dlx2 were employed to target proliferating reactive glial cells in the hippocampal region (Heinrich et al., 2011), effectively reprogramming them to differentiate into GABAergic interneurons. These newly generated neurons established GABAergic synapses with DG cells, resulting in the significant reduction in chronic seizure activity observed in MTLE-HS mice (Lentini et al., 2021). Furthermore, a recent study on gene therapy in a TLE rat model demonstrated that using AAV9 as a viral vector to express the transcription factor NeuroD1 in

Table 5 | **Transdifferentiation of astrocytes into neurons**

Glial cell	Mediating substance	Transcription factor	Transplant site	Intermediate neuron property	Disease	Research content	Application significance	Reference
Astrocytes	Retrovirus of MoMLV	Ascl1 and Dlx2	Sclerosing DG of the hippocampus	GABAergic neurons	MTLE-HS	Reprogramming reactive glial cells into GABAergic neurons and exploring the inhibitory effect of these neurons on spontaneous seizures in a mouse model of MTLE-HS.	A new potential strategy for the treatment of intractable seizures.	Lentini et al., 2021
Astrocytes	Adeno-associated virus AAV9	NeuroD1	DG area of the hippocampus	GABAergic neurons	TLE	*NeuroD1* gene therapy converted reactive astrocytes into GABAergic neurons in the hippocampus and suppressed seizures in a drug-resistant TLE rat model.	A new treatment strategy for patients with drug-resistant TLE.	Zheng et al., 2022
Myelin glial cells	CRISPR-CasRx	Ptbp1	Retina	Retinal ganglion cells	Diseases associated with RGC loss	Down-regulation of Ptbp1 by CRISPR-CasRx technology converted Müller glia to RGC in the adult mouse retina and induced neurons with a dopamine signature in Parkinson's model mice.	A new therapeutic strategy for the treatment of neurodegenerative diseases associated with neuronal loss.	Zhou et al., 2020
			Corpus striatum	Dopaminergic neurons	PD			
Astrocytes	Adeno-associated virus rAAV2/5	NeuroD1 and Dlx2	Corpus striatum	GABAergic neurons	HD	Reprogramming of striatal astrocytes into GABAergic neurons by AAV-mediated ectopic expression of NeuroD1 and Dlx2 transcription factors in the R6/2 mouse model of HD.	*In vivo* AtN transformation may be a disease-modifying gene therapy for HD and other neurodegenerative diseases.	Wu et al., 2020b
Astrocytes	NeuroD1-GFP retrovirus	NeuroD1	Cerebral cortex	Glutamate neurons	Brain injury and AD	By expressing the single neurotranscription factor NeuroD1 through retroviral vectors, reactive glial cells are directly reprogrammed into functional neurons in mouse models of brain injury and AD.	An alternative method for the repair of damaged or diseased brains.	Guo et al., 2014
Astrocytes	Small molecule compounds	NeuroD1 and Neurogenin2	Brain	Functional neurons	Undescribed	A combination of small molecules can reprogram human astrocytes into fully functional neurons, mediated by epigenetic and transcriptional regulation.	A new pathway using compounds to reprogram reactive glial cells into functional neurons is opened.	Zhang et al., 2015
Astrocytes	AAV Cre-FLEX	NeuroD1	Motor cortex	Functional neurons	Ischemic brain injury	The adenoviral vector gene therapy technology mediated by NeuroD1 converts reactive astrocytes in mice into functional neurons, promoting neural regeneration and functional recovery after ischemic brain injury.	A new therapeutic strategy for the repair after brain injury has been provided, which may effectively improve motor and cognitive functions.	Chen et al., 2020

This table provides a summary of recent experiments on the transdifferentiation of astrocytes into neurons. It outlines the basic information, key steps, transcription factors involved, and the outcomes of the transdifferentiation processes described in the literature. AAV: Adeno-associated virus; AD: Alzheimer's disease; Ascl1: achaete-scute complex like 1; AtN: astrocyte-to-neuron; DG: dentate gyrus; Dlx2: distal-less homeobox 2; GABA: γ-aminobutyric acid; GFP: green fluorescent protein; HD: Huntington's disease; MoMLV: moloney murine leukemia virus; MTLE-HS: mesial temporal lobe epilepsy with hippocampal sclerosis; NeuroD1: neurogenic differentiation 1; PD: Parkinson's disease; Ptbp1: polypyrimidine tract-binding protein 1; RGC: retinal ganglion cell; TLE: temporal lobe epilepsy.

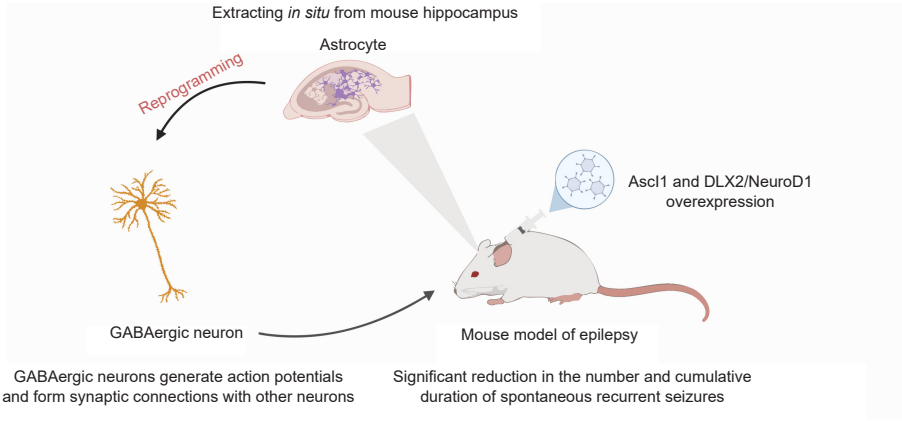

Figure 5 | ***In situ* reprogramming of astrocytes into GABAergic neurons for the treatment of epilepsy.**
This image illustrates that the directional injection of neurotranscription factors, such as Ascl1, Dlx2, and NeuroD1, into the brain can reprogram hyperactive astrocytes *in situ* into GABAergic neurons. This process effectively inhibits seizures. Created with BioRender.com. Ascl1: Achaete-scute complex like 1; Dlx2: distal-less homeobox 2; GABA: γ-aminobutyric acid; NeuroD1: neurogenic differentiation 1.

hippocampal astrocytes can successfully convert reactive astrocytes into GABAergic neurons. Immunohistochemistry, electrophysiology, and EEG analyses revealed a significant increase in the number of newly generated interneurons in the hippocampus, which formed functional synaptic connections with other neurons. This led to a reduction in the frequency of chronic seizures and improvements in cognitive and emotional dysfunction in TLE rats (Zheng et al., 2022).

Limitations

Stem cell therapy is a promising field with significant potential; however, it faces several limitations that must be addressed for future practical applications (Wojcik et al., 2024). One of the primary obstacles is the economic burden associated with these therapies. The high cost of stem cell treatments restricts their accessibility, particularly in economically disadvantaged regions, exacerbating disparities in healthcare resources and imposing additional financial strain on patients, including ongoing care expenses.

The safety and efficacy of the treatments also remain paramount concerns. The proliferative nature of stem cells, especially iPSCs, increases the risk of malignancy if they fail to fully differentiate *in vivo*, potentially leading to tumor formation (Pazzin et al., 2024). Stem cells are highly proliferative and possess the remarkable ability to self-renew indefinitely *in vitro*, differentiating into any cell type in the body upon receiving the appropriate signals (Salehpour et al., 2022). This capability is due to their unique gene expression patterns and the dynamic regulation of intracellular metabolism (Andrews et al., 2022). However, the use of stem cells in therapy carries inherent risks. If undifferentiated stem cells remain in the transplanted population, they may proliferate uncontrollably within the body, potentially leading to tumor formation. This risk is compounded by the possibility of gene mutations or epigenetic changes occurring during *in vitro* culture and manipulation, which could result in malignant transformation. Furthermore, the reprogramming process used to generate iPSCs can induce genomic instability and insertion mutations due to the use of viral vectors or reprogramming factors, further increasing the risk of tumorigenesis (Saini et al., 2023).

To mitigate these risks, it is crucial to implement rigorous strategies throughout the stem cell therapy process (Guo et al., 2024). Adhering to Good Manufacturing Practice standards during the culture and expansion of stem cells is essential to ensure their safety, effectiveness, and consistency. Regular assessments of genetic stability, such as karyotype analysis and high-throughput sequencing, should be conducted to promptly detect and eliminate cells with mutations. It is vital to rigorously implement strategies to reduce the risk of tumorigenesis. Specific culture conditions, growth factors, and co-culture techniques can be used to promote the differentiation of stem cells into target cell types while decreasing the number of undifferentiated cells (Dong et al., 2024). Techniques such as flow cytometry and magnetic bead sorting can be utilized to ensure the purity of differentiated cells and to remove any residual undifferentiated cells, further reducing the risk of tumorigenesis. Safety evaluations and monitoring after transplantation are indispensable components of the experimental process (Guo et al., 2024). Following clinical trials and treatments, patients should undergo long-term follow-up and monitoring to assess any potential tumor risks. Prior to clinical application, each stem cell therapy should be thoroughly evaluated using animal models to assess tumorigenic risks and ensure its safety for human use (Andrews et al., 2022).

Another major challenge faced in the use of stem cell therapy is ensuring the long-term survival and differentiation of stem cells into functional neurons within the host body after transplantation. Existing research indicates that the survival rate of transplanted stem cells is relatively low, and the proportion that differentiate into functional neurons is also limited (Kim et al., 2024). This restricts the efficacy of stem cell therapy in the treatment of epilepsy. Additionally, the transplantation of allogeneic stem cells (e.g., from umbilical cord blood or bone marrow) may involve challenges such as immune rejection, which can lead to transplant failure. Ensuring the safety and viability of stem cells is a critical issue in clinical research.

The sourcing of stem cells presents another significant challenge. While the application of iPSCs reduces some of the ethical controversies associated with ESCs, the risks of gene insertion and mutations during the cell reprogramming process may still hinder their clinical application (Zhang et al., 2024a). Furthermore, MSCs can be derived from various sources, including bone marrow, adipose tissue, and umbilical cord blood, each conferring distinct characteristics in terms of quantity, quality, and differentiation potential (Alayli et al., 2023). This complexity adds to the challenges of stem cell preparation; for instance, extracting stem cells from bone marrow requires extensive separation and purification steps, and the limited cell yield makes it difficult to meet the demands of large-scale clinical applications (Han et al., 2019).

The ethical and societal issues surrounding stem cell research, particularly with ESCs, pose significant hurdles. This research is often met with controversy (Zhou et al., 2024b) due to its association with human embryos (Danačíková et al., 2024), which sparks intense bioethical debates. hESCs have been the subject of significant controversy since their discovery. One of the primary ethical considerations is that if an embryo is implanted into a woman's womb with the appropriate hormonal support, it has the potential to develop into a live-born human being (Ju et al., 2024). The use of hESCs in scientific research and medical treatment raises ethical concerns, particularly because acquiring these cells necessitates the destruction of the embryo. Critics argue that this process is ethically objectionable, since it involves terminating potential human life. Conversely, advocates of hESC research argue that the potential benefits, such as developing therapies for debilitating diseases like retinal degenerative conditions, justify their use (Khandia et al., 2024). To address these ethical concerns, various countries have established guidelines for stem cell research (Lahiry et al., 2019). For instance, embryos should not be cultured beyond 14 days, which is the point at which neural precursors begin to develop. Participants in research studies should have the right to decline participation at any time, and research involving the transplantation of human stem cells into animal models should be strictly monitored. When stem cell approaches are translated into clinical treatments, ethical standards must be adhered to in order to ensure the safe manufacturing and responsible use of viral pathogens or cell lines containing genetic disorders. Additionally, it is crucial to consider how much information should be provided to patients undergoing stem cell therapy to ensure that critically ill patients are not misled with unproven cures (Pennings and Van Steirteghem, 2004). Regarding iPSCs, these cells are created by genetically reprogramming adult cells to resemble ESCs (Liu et al., 2020). This method of obtaining stem cells raises fewer ethical concerns, as it does not require the use or destruction of embryos, making it more morally acceptable to many people (Song et al., 2024). Moreover, iPSCs can be derived from an individual's own cells, reducing the risk of immunological rejection and eliminating ethical issues related to donor consent (Waris et al., 2024b). However, ethical questions remain

regarding the long-term safety of using genetically edited cells and the potential for unforeseen consequences (Zhang et al., 2016). It is important for researchers and clinicians to continue addressing these ethical considerations as they develop and implement stem cell therapies.

We acknowledge that this review has certain limitations. First, while we have made extensive efforts to search and screen the relevant literature, it is possible that some recent or lesser-known studies on stem cell therapy for epilepsy may have been overlooked due to the vast amount of information available and the evolving nature of this field. Second, most of the studies included in this review are in the preclinical or early clinical trial stages, which limited our ability to draw definitive conclusions regarding the efficacy and safety of stem cell therapies for epilepsy in humans. Furthermore, while our review focuses primarily on stem cell-based therapies, it may not cover all aspects of epilepsy treatment, including pharmacological or surgical interventions. Lastly, the economic and practical challenges associated with stem cell therapy, such as the high costs and limited cell yield, are important factors that could restrict its widespread application in clinical practice. Nonetheless, we believe this review provides a comprehensive overview of the current state of research on stem cell therapy for epilepsy and highlights the potential advantages of this therapeutic approach.

Discussion

The rapid advancements in stem cell technology have unveiled new avenues for improving the pathophysiology of epilepsy patients and exploring its underlying mechanisms. Experiments using animal models have demonstrated that stem cell grafts can not only inhibit excessive neuronal activity and control seizures but also exhibit neuroprotective and regenerative properties (Patil et al., 2024). These findings have heightened expectations for overcoming significant barriers in epilepsy treatment and accelerating the development of cell replacement therapies in clinical trials.

The therapeutic effects of MSCs are primarily attributed to their nutritional support, particularly their capacity to produce extracellular vesicles and secrete a range of cytokines and growth factors (Zhou et al., 2024a). Preclinical experiments have used various cell types, including genetically modified MSCs, to investigate their potential therapeutic efficacy. Clinical trials have shown that patient-derived MSCs can effectively reduce the frequency of epileptic seizures and enhance neurological, cognitive, and motor functions (Szczepanik et al., 2020; Milczarek et al., 2024). More details can be found in **Table 1** and **Additional Table 1**. NSCs possess the ability to secrete multiple neurotrophic factors, including brain-derived neurotrophic factor and GDNF, and exhibit immunomodulatory properties (Hattiangady et al., 2020). These cells can be cultured *in vitro* and induced to differentiate into specific cell types. The transplantation of NSCs offers a novel approach to epilepsy treatment by replacing lost inhibitory interneurons. ESCs exhibit robust self-renewal capabilities and the potential to differentiate into all types of somatic cells. In the context of epilepsy treatment, ESCs can facilitate neuron regeneration, maintain cellular homeostasis, and promote restorative therapies through induced directional differentiation (Bershteyn et al., 2023; Zhu et al., 2023). A promising therapeutic strategy involves differentiating ESCs into GABAergic neurons for transplantation into epileptic lesion sites. This approach is currently being evaluated in clinical trials and holds promise as a breakthrough treatment for refractory epilepsy, with further information summarized in **Additional Table 1**. iPSCs, which share the same genetic background as the donor, provide a means to reduce the risk of immune rejection and address ethical concerns. By utilizing iPSCs, patient-specific neurons that mimic epileptiform hyperactivity can be generated, offering a valuable platform for in-depth research into the mechanisms of epilepsy and for testing AEDs (Song et al., 2024). The advent of iPSC technology has revolutionized regenerative medicine, particularly in the field of organoids (Gross, 2022). Although research on iPSC-based cell therapy for epilepsy is still in the preclinical stage, its potential cannot be overlooked. Furthermore, ongoing research is exploring the reprogramming of astrocytes to transdifferentiate into neurons (Chen et al., 2020). Despite some controversy in this field, this approach presents new ideas and possibilities for the treatment of epilepsy.

iPSCs derived from a patient's own body cells have the theoretical potential to differentiate into any somatic cell type, offering opportunities for creating patient-specific models and enabling personalized cell therapies (Meissner et al., 2022). Dinesh Upadhya and colleagues demonstrated the therapeutic potential of this approach by transplanting human iPSC-derived MGE-like interneuron precursors into the hippocampus of rats with TLE. This intervention effectively suppressed epilepsy symptoms and alleviated cognitive, memory, and emotional dysfunction during the chronic phase of the disease, underscoring the promise of patient-specific MGE cell transplantation for clinical applications (Upadhya et al., 2019a). Moreover, combining iPSC technology with gene editing techniques, such as the personalized adenine base editor approach developed by Konishi et al. (2024) and colleagues, presents unique advantages in treating hereditary epilepsy. Konishi et al. (2024) successfully modeled Neuroterpenoid Inclusion Body Familial Encephalopathy, a rare autosomal dominant progressive myoclonic epilepsy, using HEK293T cells and iPSCs. By accurately correcting pathogenic variants, they effectively prevented neuronal death caused by cytotoxic aggregation. The most straightforward and definitive approach to preventing immune rejection of inhibitory interneurons implanted in cases of HLA mismatch is to cultivate these interneurons from iPSCs derived from the patient themselves (Beaudreault et al., 2024). However, despite these promising developments, the application of iPSCs in the treatment of epilepsy remains limited to a few clinical trials.

In recent years, a primary research focus has centered on strategies aimed at differentiating stem cells into cINs. These neurons play a crucial role in maintaining the balance of neural networks by modulating neuronal activities, thereby suppressing the hyperexcitable networks characteristic of epilepsy. Studies have demonstrated that promoting the conversion of stem cells into cINs through various induction methods in vitro, followed by transplantation into damaged brain regions, can effectively control seizure events (Bershteyn et al., 2023; Zhu et al., 2023). Compared to current treatment strategies (Gonzalez-Ramos et al., 2024), epilepsy cell therapy provides enhanced inhibition in an activity-dependent manner, avoiding the systemic adverse effects of anti-seizure medications and the damage to healthy neural tissue caused by surgical resection of lesions. Currently, clinical research on stem cell therapy for epilepsy is predominantly characterized by small scale and short duration, lacking comprehensive long-term follow-up and a substantial number of samples (Terman et al., 2024). To address this, future research endeavors should focus on large-scale and prolonged clinical studies to rigorously validate the efficacy and safety of stem cell therapy.

Furthermore, the transplantation of cINs has shown significant efficacy in reversing comorbid behavioral abnormalities associated with epilepsy, such as anxiety, depression, and cognitive deficits in preclinical studies (Kim et al., 2024). The transplanted cINs can survive long-term in the inflammatory environment of the host's epileptic brain, allowing them to integrate into neural circuits and exert their therapeutic effects. This stem cell-derived cIN transplantation could also be utilized to treat various other brain diseases associated with impaired circuit inhibition, including neuropathic pain, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, autism spectrum disorders, and schizophrenia (Zhu et al., 2023). The survival rate following stem cell transplantation is a pivotal factor influencing its therapeutic outcome (Rahimi Darehbagh et al., 2024). Future research should explore novel transplantation methodologies and advancements (Roslan et al., 2024). Specifically, enhancing the pretreatment and culture conditions of stem cells, along with refining the transplantation route and dosage, can significantly improve differentiation efficiency.

The application of organoids in epilepsy research has provided a novel perspective for understanding and treating the disease. By mimicking developmental processes in the brain, organoids offer a powerful tool for investigating the mechanisms underlying epileptogenesis (Brown et al., 2024). The creation of more sophisticated and patient-specific organoids is becoming increasingly feasible. Researchers aim to improve the survival and differentiation rates of these organoids—and thereby enhance their therapeutic potential—by optimizing the pretreatment and culture conditions of the stem cells used to generate them and by refining transplantation techniques (Rossi et al., 2018). Additionally, with the continuous advancement of genetic testing technologies, the etiology of epilepsy can be more precisely determined, paving the way for the development of personalized treatment plans based on individual genetic information (Clevers, 2016). These personalized treatment plans are designed

to enhance therapeutic efficacy, reduce side effects, and improve patients' quality of life.

Personalized medical care represents a tailored approach to treatment, where medical interventions are customized based on a patient's unique clinical, genetic, and environmental characteristics (Chan and Ginsburg, 2011). This approach offers significant advantages over traditional medicine, as it allows for the optimization of therapies to enhance safety and effectiveness while minimizing adverse reactions. By taking into account an individual's biological information, personalized medicine has the potential to significantly improve patient outcomes (Facklam et al., 2020). The advent of iPSCs has greatly advanced personalized medical care, particularly in the field of nervous system diseases. Researchers can now reprogram patients' somatic cells into iPSCs, which can then be further differentiated into nerve cells or other relevant cell types to create personalized cell models (Del Carmen Ortuño-Costela et al., 2019). These models are invaluable for disease modeling, drug screening, and gene modification, as they are derived from the patient's own cells and therefore retain unique genetic and epigenetic characteristics. iPSCs offer distinct advantages over other cell types, such as ESCs, as they avoid ethical concerns and provide high immune compatibility. Furthermore, the development of organs-on-chip technology has provided a powerful tool for personalized disease modeling and drug screening (Ma et al., 2021). These microfluidic devices emulate the functionality and physiological environment of human organs, allowing for precise control over culture conditions and cell patterning (Wu et al., 2020a). Additionally, parameters such as flow rate, pressure, oxygen levels, and pH can be controlled, leading to consistent culture conditions (Wu et al., 2020a). The combination of iPSC technology with organ-on-chip systems has the potential to revolutionize the personalized evaluation of drug-induced toxicity, integrating the patient specificity of iPSCs with a 3D model that mimics in vivo tissue characteristics. For example, Bircsak et al. developed an automated 3D microfluidic liver chip called OrganoPlate-LiverTox, which was used to screen for hepatotoxicity in Qualcomm's compounds (Bircsak et al., 2021). This approach combines the patient specificity of iPSCs with the physiological relevance of a 3D model, providing a more accurate representation of in vivo tissue characteristics. In the near future, this technology is expected to be applied in the field of epilepsy, where personalized cell models and organ-on-chip systems could be used to investigate the pathophysiology of epilepsy, test new therapies, and evaluate drug toxicity in a patient-specific manner.

Another promising approach in personalized medical care involves utilizing gene editing technology, such as CRISPR-Cas9, to modify stem cells prior to transplantation (Tyumentseva et al., 2023). This technique allows for the repair of gene mutations that cause diseases like epilepsy or the enhancement of the therapeutic effects of the cells. By customizing the transplanted cells to match the specific conditions of individual patients, a higher level of personalized treatment can be achieved (Chen et al., 2024b). CRISPR/Cas9 has emerged as a powerful gene-editing tool, capable of correcting harmful base mutations with high precision.

Over the years, various Cas9 variants have been developed to address the complex genomic changes that occur during diseases. In preclinical studies, researchers have demonstrated the efficacy of modifying genes associated with neurological disorders, such as tau for Alzheimer's disease (Wegmann et al., 2021) and huntingtin for Huntington's disease (Agustín-Pavón et al., 2016), providing proof-of-concept for their potential therapeutic applications. In another groundbreaking study, Ababneh et al. (2020) used CRISPR-Cas9 to delete the C9orf72 repeat region in an iPSC line derived from an ALS patient. This modification led to improvements in the pathological phenotypes of iPSC-derived motor neurons, highlighting the potential of gene editing in treating neurodegenerative diseases. The field of genetic medicine took a historic step forward in 2023 when the FDA granted approval for the first CRISPR-based therapy for sickle cell disease (Philippidis, 2023). This milestone marks a significant advancement in genetic medicine, offering patients renewed hope for effective treatments.

In summary, stem cell therapy holds promising potential in the management of epilepsy, offering new treatment options for patients who have not responded to conventional therapies. Despite the challenges that remain, ongoing research and technological innovations in this field have the potential to significantly improve treatment outcomes and quality of life for individuals with epilepsy. The continued advancement in stem cell therapy provides hope for the development of more effective and personalized treatment options in the future.

Author contributions: *WJ and ZS designed the review. XM, ZW, YN, JZ, and XW contributed to writing the manuscript. WJ, FY, DW, XW, and ZS revised the manuscript. All authors approved the final version of the manuscript.*
Conflicts of interest: *The authors declare that they have no conflict of interest related to this manuscript.*
Data availability statement: *All relevant data are within the paper and its Additional files.*

Additional file:
Additional Table 1: *Clinical trials of stem cell therapy for epilepsy.*

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