




# Stem cell therapy in neurological disorders: promises and concerns

Said Hachimi-Idrissi<sup>1,2,3\*</sup> 

<sup>1</sup>Department of Emergency Medicine, Ghent University Hospital, B-9000 Ghent, Belgium

<sup>2</sup>Faculty of Medicine and Health Sciences, Ghent University, B-9000 Ghent, Belgium

<sup>3</sup>Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, 1090 Brussels, Belgium

**\*Correspondence:** Said Hachimi-Idrissi, Department of Emergency Medicine, Ghent University Hospital, Corneel Heymanslaan 10, B-9000 Ghent, Belgium. [said.hachimiidrissi@ugent.be](mailto:said.hachimiidrissi@ugent.be)

**Academic Editor:** Silvia Fischer, Justus-Liebig-University, Germany

**Received:** March 29, 2023 **Accepted:** August 17, 2023 **Published:** October 31, 2023

**Cite this article:** Hachimi-Idrissi S. Stem cell therapy in neurological disorders: promises and concerns. *Explor Neuroprot Ther.* 2023;3:346–62. <https://doi.org/10.37349/ent.2023.00055>

## Abstract

Self-neuronal regeneration is often limited or nonexistent after neuronal cell damage, making new technologies necessary for treating neurological damage. Although the brain can partially compensate by increasing its plasticity, these compensatory mechanisms can never fully restore the pre-damage state. Analysis of the literature regarding stem cell therapy in case of neurological disorders. Stem cells have shown promise for treating various neurological disorders and disabilities due to their regenerative capacity. Transplanting or administration of different types of stem cells has yielded promising results in animal models and early clinical trials. However, concerns remain regarding their implementation. The type of stem cell used, the optimal method and route of administration, the number of stem cells administered, preconditioning, and the injection schedule all need to be determined. Additionally, the long-term safety of stem cell treatment and the recipient's age requires further investigation. Despite these concerns, stem cell therapy holds tremendous promise for treating neurological disorders, and continued research and well-designed studies will be crucial for unlocking its full potential.

## Keywords

Neural stem cells, embryonic stem cells, induced pluripotent stem cells, adult mesenchymal stem, quantity, route of administration, graphene, neurological disorders

## Introduction

Despite its sophisticated nature, the central nervous system remains mysterious and difficult to understand. Many disorders that affect the central nervous system can lead to irreversible impairments and are often associated with cognitive and physical disabilities.

Unfortunately, the adult brain has limited ability to self-regenerate when it is damaged, making it difficult to achieve full recovery. Although there is some potential for endogenous regeneration in the central nervous system, it is not enough to achieve complete recovery. Furthermore, pharmacological

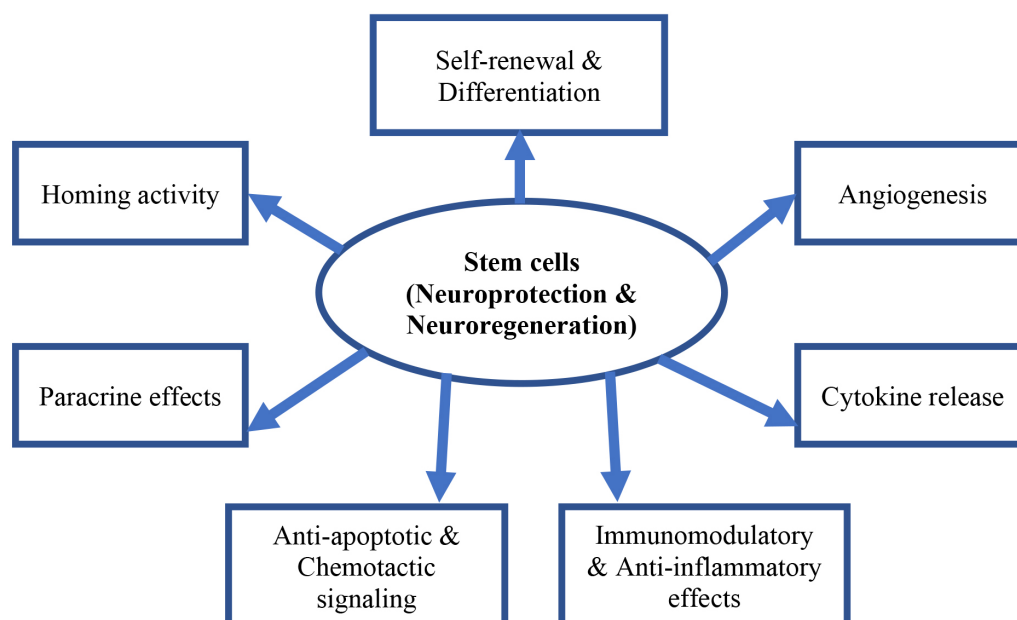


therapies that could address the underlying disease processes are rare and often come with inherent drawbacks, such as temporary efficacy, lack of full neurological recovery, or overwhelming cost [1].

Therefore, new therapeutic approaches need to be explored to address brain damage related to central nervous system disorders or diseases. Stem cell therapy has opened new possibilities for treating several neurological disorders. Due to their ability to regenerate and repair, stem cell therapy appears to be a promising candidate for achieving full neurological recovery. Animal studies have shown improvements in neurological function through restorative processes [2]. In stroke and Parkinson's disease, some recovery has been observed through plasticity and brain remodeling [2]. The mechanism of action of cell therapies is different from drugs. Drugs such as "recombinant tissue plasminogen activator" have a therapeutic role only during a narrow time window and are associated with potential risks, even lethal ones. Stem cell therapies have different mechanisms of action and a wider therapeutic time window [3].

## The mechanisms of action, the types, and the properties of stem cells as their potential therapeutic approach in neurological disorders

Overall, stem cells have unique properties that make them valuable in regenerative medicine and the treatment of various diseases and injuries. Their ability to differentiate into multiple cell types, migrate to damaged areas of the body, and secrete growth factors make them a promising tool for repairing and regenerating tissues and organs [4]. Upon transplantation, stem cells can migrate and home toward injured areas of the brain, a process attributed to the expression of growth factors and chemokines [4]. Once at the site of injury, stem cells differentiate into host tissue cells, replacing injured and necrotic neuronal tissue [5]. Through their paracrine mechanisms, stem cells further reduce injury and stimulate endogenous cells to repair and restore the normal functioning of neurons [6]. Additionally, stem cells secrete an array of neuroprotective growth factors that activate several signaling pathways, thereby enhancing differentiation, survival, and maintaining neuronal functions [7]. Also stem cells have angiogenesis, immunomodulatory, and anti-inflammatory paracrine functions by producing growth factors and interleukin [8, 9] (Figure 1).



**Figure 1.** Potential therapeutic actions of stem cells as "neuroregenerative and or neuroprotective" effect in neurological disorders

*Note.* Adapted from "Stem Cell Therapy in Pediatric Neurological Disabilities" by Sharma A, Sane H, Gokulchandran N, Badhe P, Kulkarni P, Pai S, et al. In: Uner Tan, editor. Physical Disabilities. United Kingdom: IntechOpen; 2017. (<http://dx.doi.org/10.5772/67656>). CCBY.

The properties mentioned in [Figure 1](#) are crucial when considering stem cell transplantation for brain damage. Stem cells possess the remarkable ability to both self-renew and differentiate into multiple cell lineages [10]. There are various types of stem cells, including neural stem cells (NSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult mesenchymal stem cells (MSCs).

### NSCs

Originate primarily from the subventricular zone and sub-granular zone of the hippocampal dentate gyrus. During embryonic development of the central nervous system, NSCs give rise to neurons, astrocytes, and oligodendrocytes [11]. *In vitro*, self-renewing NSCs can generate these same cell types [12]. Additionally, derived neurons can be supported for prolonged culture using growth factors such as epidermal growth factor [13], fibroblast growth factor-2, and brain-derived neurotrophic factor [14].

These properties enable *in vitro*-cultured NSCs to undergo self-renewal and differentiation into various types of neurons and glial cells. NSC transplantation therapies are based on these unique properties [11].

### ESCs

ESCs are obtained from the inner cell mass of the blastocyst and can differentiate into all three germ layers due to their pluripotent activities. Therefore, they have been the focus of research as a treatment for different neurological diseases. After transplantation, they can differentiate into neurons and glial cells [15] as well as exhibit long-term stability allowing them to integrate the neurological circuitry [16]. By secreting neurotrophic factors, ESCs have a trophic effect on neuronal regeneration at the injured site [17].

Neurons derived from ESCs and possessing appropriate cortical identity have the potential to contribute to the reconstruction of damaged cortical circuitry of the same areal identity [18]. This has been demonstrated in studies using medial ganglionic eminence-like progenitor cells and retinal progenitor cells differentiated from ESCs, where their regenerative potential has shown improvement in learning and memory in Alzheimer's disease, as well as the structure and function of the retina in retinal degenerative diseases [19, 20].

### iPSCs

iPSCs are laboratory-engineered cells that mimic ESCs by converting tissue-specific cells, like skin cells, into pluripotent cells that can give rise to all cell types in the body. While iPSCs share many similarities with ESCs, they are not the same. The successful induction of somatic cells into iPSCs is a significant milestone in stem cell and regeneration research.

Takahashi and Yamanaka [21] first achieved the induction of pluripotent stem cells from mouse embryonic and adult fibroblasts by introducing four factors (*Oct3/4*, *Sox2*, *c-Myc*, and *Klf4*) under ESC culture conditions. Yu et al. [22] later established another induction method for iPSCs using a combination of *Oct4*, *Sox2*, *Nanog*, and *Lin28*. iPSCs generated from both methods were similar to ESCs in terms of morphology, proliferation, expression of cell-surface markers, and gene expression profiles.

Takahashi et al. [23] also successfully induced iPSCs from human dermal fibroblasts using the same four factors. These iPSCs were able to generate three germ layers *in vitro* and in teratomas, demonstrating their potential as a candidate for cell therapy. Other cells, such as hepatocytes, circulating T lymphocytes, and keratinocytes, have also been reprogrammed into iPSCs [24].

The potential uses of iPSCs range from constructing disease models to patient-specific therapeutic transplantations [25]. The availability of iPSCs from patients suffering from a particular neurological disease is already contributing to the development of better disease models. An iPSC-based model for neurodegenerative diseases such as Alzheimer's disease has been established [26], and iPSC derivatives have been used to investigate the pathogenesis of retinal degenerative diseases [27]. Transplantation of human iPSC derivatives has shown promising results in some neurological disease models, such as spinal cord injury (SCI) [28], intracerebral (IC) hemorrhage [29], and retina-related diseases like macular degeneration [30]. Overall, iPSCs have the potential to revolutionize the field of regenerative medicine and offer new avenues for understanding disease pathogenesis and developing effective therapies.

## MSCs

MSCs are pluripotent stem cells especially located in connective tissues, also called mesenchymal stromal cells. First discovered in human bone marrow [31] but can also be isolated from various human tissues such as peripheral blood, adipose tissue, muscle, skin, placenta, and amniotic fluid [32, 33]. Researchers discovered that MSCs can differentiate into cell types of all three germ layers [32]. This makes MSCs a therapeutic source for various neurological diseases. Their neurogenic and immune-modulatory properties make them a suitable cure for different neurological disorders [34]. In fact, autologous bone marrow-derived MSC treatments for Parkinson's and Alzheimer's diseases, have shown tremendous therapeutic efficacy [35, 36].

Indeed, MSCs have many advantages: easily accessible; no tumoral formation; easy to cross blood-brain barrier (BBB), and no ethical issue regarding their clinical use. Other advantages also of great importance are the tropism of MSCs not only to attract other MSCs, and to migrate to the cerebral lesion site, but also to activate signaling pathways to promote paracrine secretion of cytokines and growth factors.

MSCs display vasculogenesis and neuroprotective properties making them a suitable candidate for cell transplantation in neurological disorders. Also, due to their immune suppressive capability, no immunological rejection should be expected as well as their ability to be transplanted across the allogenic barrier [37–39].

Despite the advantages mentioned above, the application of stem cell therapy using MSCs remains limited. MSCs have shown a low survival rate, limited engraftment to damaged areas, as well as low differentiation into fully functional tissues [40]. Studies have suggested that their potential beneficial effect is primarily due to their trophic effect rather than the replacement of damaged or lost brain tissue [37, 41]. Additionally, bone marrow MSCs have an anti-inflammatory and immunomodulatory role [38, 41]. However, there is currently no evidence that transplanted MSCs, even if transdifferentiated into neurons, can integrate into the neuronal circuitry of the host nervous system [41].

## Stem cell as a therapeutic approach in neurological disorders

Neurodegeneration leads to a gradual deterioration of brain functionality secondary to neuronal and other cell loss of the central nervous system [42]. Stem cells when used as a therapeutic approach could salvage neurons from deterioration and enhance repair of the damaged brain's circuitry [43]. In this paragraph, different types of stem cells used as a therapy for neurological disorders and diseases will be briefly highlighted, also some promises and concerns will be discussed.

Diseases such as Parkinson's [44], Huntington's [45], ischemic stroke [46], traumatic brain injury (TBI) [47], amyotrophic lateral sclerosis [48], Multiple sclerosis [49], Alzheimer's [50], SCI [51] have been used as a targeted treatment for stem cell therapy.

It is highlighted in [Table 1](#) the use of different types of stem cell therapy, the model used whether animal or clinical studies (only the published clinical studies are reported), the number of stem cells transplanted, the route of administration as well as the potential beneficial effects and the risks.

NSCs obtained from fetal brain tissue can differentiate into multiple cell types, but they are primarily committed to the neuronal lineage. Unfortunately, these cells are both difficult to obtain and often present in limited quantities [52].

Administration of NSCs in animal models improved dyskinesia in Parkinson's, reduced lesions in Huntington's disease, reduced the lesion size in stroke and TBI, enhanced synaptogenesis, and improved learning memory in Alzheimer's disease, and increased life span in amyotrophic lateral sclerosis. In human small studies, the use of NSCs seemed to be safe ([Table 1](#)).

ESCs are pluripotent in nature and could restore brain injuries and neurodegeneration, however, tumor formation restricts their widespread application [37].

**Table 1.** Preclinical and clinical studies of stem cell transplantation in neurological disorders

Type of stem cells	Neurological disorders	References	Models	Administration's route	Quantity of stem cells	Effects	Risks
NSCs	Parkinson's disease	[41, 44]	Rats	IV, IC	$2 \times 10^6$ cells	Ameliorated Parkinson dyskinesia and promoted neurogenesis	Risk of cancer development
	Huntington's disease	[96]	Primate, rats	Transplanted into brain	$5 \times 10^4$ – $1 \times 10^6$ cells	Reduction of lesion size and proliferation in the striatum	
	Stroke	[45]	Mice	Transplanted into brain	$2 \times 10^5$ cells	Improved sensorimotor functioning and reduced infarct size	
		[97]	Human	IC	$2 \times 10^6$ cells	It has been shown to be safe and effective in improving NIHSS scale	
				IV	Escalation dose from $3 \times 10^5$ – $1 \times 10^7$ cells	Induces neurogenesis in the human brain	
	TBI	[46]	Mice	Transplanted into brain	$2.5 \times 10^5$ – $2 \times 10^7$ cells	Early transplant showed an enhanced functional recovery, while a delayed transplantation seems to be more controversial	
	Amyotrophic lateral sclerosis	[47]	Mice, rats	IV	$2.5 \times 10^5$ – $1 \times 10^6$ cells	Increased life span, improvement in motor neuron survival and slow down disease progression	
[98]		Human	Transplanted in the spinal cord, transplanted in the motor frontal cortex	$5 \times 10^6$ – $1.6 \times 10^7$ cells	Improved the life span and reduced disease progression		
	Alzheimer's disease	[99]	Rats, mice	Transplanted into brain	Rats: $1 \times 10^5$ – $1 \times 10^6$ cells; mice: $1.5 \times 10^4$ cells	Enhanced synaptogenesis and improved learning and memory	
ESCs	Parkinson's disease	[100]	Mice, rats, monkey	IC	Mice: $1.5 \times 10^5$ cells; rats: $2.5 \times 10^5$ cells; monkey: $7.5 \times 10^6$ cells	Neuroprotection and neurogenesis	Tumor formation; ethical issue
	Huntington's disease	[101]	Mice	Transplanted into brain	$1 \times 10^5$ cells	Reduction in cerebral lesion size and proliferation in the striatum	
	Multiple sclerosis	[101]	Mice, rats	Intraventricular	$1 \times 10^6$ cells	Consistent beneficial effect	
				Human	IV	Not specified	Inconsistent results
	Alzheimer's disease	[19, 20, 102]	Mice, rats	Transplanted into brain	$1 \times 10^5$ – $1 \times 10^6$ cells	Improved learning and memory	
iPSCs	Parkinson's disease	[103]	Mice	Transplanted into brain	$1.5 \times 10^5$ cells	Neuroprotective and neurogenesis	Risk of cancer and teratoma formation
	Huntington's disease	[45, 104, 105]	Rodent	IV, transplanted into brain	$1 \times 10^6$ cells	Migration to striatum and differentiation into glial cells	
	TBI	[56]	Rats	IV	$2 \times 10^6$ – $1 \times 10^7$ cells	Long-term improvement in spatial learning and	

**Table 1.** Preclinical and clinical studies of stem cell transplantation in neurological disorders (*continued*)

Type of stem cells	Neurological disorders	References	Models	Administration's route	Quantity of stem cells	Effects	Risks
MSCs	Amyotrophic lateral sclerosis	[57]	Mice	In culture cells as well as in mice	$1 \times 10^6$ cells	attenuation of neuroinflammation Increased life span	
	Alzheimer's disease	[26]	Transgenic mice	Transplanted into brain	Not specified	Reduction of brain amyloid beta	
	Parkinson's disease	[36]	Human	IV	$1 \times 10^6$ cells	Exert therapeutic effect by protecting dopaminergic neurons and maintaining the nigrostriatal pathway	Short survival time of the cells; homing issues
		[106]	Mice	Transplanted into brain	Not specified	Subjective improvement of the gait and the facial symptoms	
	Stroke	[66] [67]	Mice, rats Human	IC, IV IV	$1 \times 10^8$ cells	Improved sensorimotor functioning and reduced infarct size	
	TBI	[107]	Rats	Transplanted into brain	$3 \times 10^5$ – $4 \times 10^6$ cells	Reduced inflammatory cytokines, reactive astrogliosis, and edema	
	Amyotrophic lateral sclerosis	[38, 108]	Human, mice	IV	$1.7 \times 10^7$ cells	Positive safety outcome and increased life span	
	Multiple sclerosis	[48]	Mice, rats	Transplanted into brain	$2 \times 10^7$ cells	Alleviated symptoms and positive effect on cytokines	
		[38]	Human	IV	$2.5 \times 10^6$ cells	Safe and improvement of symptoms	
	Alzheimer's disease	[35]	Mice	Intracerebroventricular, IC, IV	Not specified	Improved cognitive function and reduced amyloid beta	
SCI	[64] [51]	Rats Human	IC, IV IV	Not specified $8 \times 10^5$ – $4 \times 10^8$ cells	Improve motor recovery Improve sensory and motor score		

IV: intravenous; NIHSS: National Institutes of Health Stroke Scale

In the preclinical setting, ESCs displayed neuroprotection and neurogenesis in Parkinson's disease, reduced cerebral lesions in Huntington's disease, and improved learning and memory. However, in a clinical setting, the results seemed inconsistent (Table 1).

iPSCs have become a widely available resource for research as various iPSC cell lines are being produced in bulk and are commercially available. The use of poly(ADP-ribose) polymerase-1 (PARP-1) to produce iPSCs has been shown to be effective in reducing the risk of tumor formation [53]. However, the teratoma formation risk has not been completely eliminated.

iPSC can be derived from various somatic cells of the body, including peripheral blood cells, hepatocytes, stomach cells, and keratinocytes [54]. Interestingly, even a small blood quantity as low as just 10  $\mu$ L drawn from fingertips can be used to generate iPSCs [55].

Patient-derived iPSCs are widely used for modeling various human neurodegenerative diseases [56, 57]. For instance, spinal muscular atrophy has been efficiently modeled *in vitro* using patient-derived iPSCs, which accurately depict the disease phenotypes [58]. However, iPSCs do have a few limitations. Neurodegenerative disorders are generally late-onset diseases, and their symptoms begin to manifest with

increasing age. Thus, modeling such diseases via animal models is not only time-consuming but also costly. However, when somatic cells are reprogrammed back into an embryonic-pluripotent-like state, which enables them to develop into any human cell, they lose the age-associated features [59]. During this transformation process, iPSCs undergo rejuvenation, and their embryonic pluripotent state is re-established. It has been reported that even aged donor-derived iPSCs undergo rejuvenation, displaying a loss in markers of senescence, enhanced mitochondrial fitness, and increased telomere length [59]. However, patient-derived iPSCs still lack the age-related phenotypes necessary for effectively modeling late-onset neurodegenerative diseases. Nevertheless, this hurdle has been largely overcome by progerin-induced aging in iPSCs [60].

Studies in rodents have displayed an improvement in memory, neuroprotection, and increased lifespan in Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis diseases (Table 1).

MSCs multipotent cells also find widespread application because they are immunomodulating in nature. These immunomodulating characteristics allow them to escape the host's immune system surveillance and hence successful transplants without the use of immunosuppressant drugs and avoiding immunosuppressant drug side effects [61].

Other studies have shown that MSCs may be beneficial in SCI through direct contact with immune cells or paracrine-release signaling molecules to reduce the inflammatory response at the level of the injured spinal cord. Also, MSCs release neurotrophic factors such as BDNF and b-NGF to promote axon regeneration. Furthermore, MSCs regulate signaling pathways to inhibit glial scarring. Hence, mitigation of glial scarring facilitates axon regeneration and thereby improves the sensory and motor scores [62].

In preclinical studies, the use of stem cell therapy improved sensorimotor functioning, reduced inflammatory cytokines, alleviated symptoms, and improved cognitive function in stroke, SCI, TBI, multiple sclerosis, and Alzheimer's disease respectively (Table 1).

Despite a number of animal experiments, the data generated fails to be translated into human diseases [63]. The lack of translational implementation could be explained by several issues: the quality of the studies, the type of the animal model, the therapeutic modalities, timing, preconditioning, etc. [51, 63, 64].

## Study quality and the animal model

The considerable degree of heterogeneity of the disease phenotype in clinical settings when compared to homogeneity in animal studies, is an affirmation of the lack of standardization (Table 1). The non-confirmation of the positive preclinical studies in humans could partially be explained by the limited number of patients included and the heterogeneity of the studied population [63]. Also, a lack of blinding because of ethical considerations [63]. Equally important is the choice of the animal model as a therapeutic target. Most studies were using rodents as an animal model [65]. We should question whether rodents could be a good model or even any animal model would be appropriate to mimic the clinical setting. Even using a high phylogenetic species such as nonhuman primates remains an issue. These animal models require laborious post-operative care, are a homogenous population in contrast to humans, and do not have underlying co-morbidities.

Several steps have been taken to standardize preclinical studies, as proposed in the Stem Cell Therapy as Emerging Paradigm in Stroke (STEPS) initiative [66, 67]. However, some researchers argue that certain issues related to the translation of stem cell therapy to human patients may be better addressed through careful studies in human models, rather than additional preclinical studies [65].

## Cell type

When transplanting stem cells, the choice between autologous and allogeneic stem cell transplantation should be carefully considered, considering the risks and benefits for each patient. The use of allogeneic stem cells implies the risk for immune reactions and graft-versus-host disease which automatically require immunosuppressants. The choice of autologous stem cell transplantation eliminates the risk of immune reactions and graft-versus-host disease, but it may not be possible for all patients.

Manufacturing steps for stem cell transplantation, such as genetic modification, cell expansion, and reprogramming (using viral integration) should be carefully controlled to minimize the risk of tumor formation [68]. This requires stringent quality control measures and adherence to good manufacturing practices. The time and requirements for cell expansion may differ between cell types and medicinal manipulations, which may affect the availability and cost of stem cell therapies. These factors should be carefully considered when developing and implementing stem cell therapies [69, 70].

## Dose of stem cells administered

When evaluating animal studies, often a higher cell concentration was used (ranging from  $5 \times 10^6$  to  $5 \times 10^7$ ) [71–73]. Others proposed 2 different administrations rather than one single administration [74]. But here, it seems that the benefit might reside in the absolute higher dose caused by the double injection, rather than the number of injections itself.

According to the literature, a single high concentration of  $3 \times 10^6$  cells is considered better than multiple low-dose injections at different times [75]. The cell concentration-response curve probably follows a U-shape rather than a linear progression, with a higher number of cells leading to a ceiling effect. One study described a severe ipsilateral eye inflammation followed by acute mortality of the studied animals after administration of  $10^7$  cells.

Besides the cell concentration, the type and the size of cells are of great importance. MCSs have the tendency to aggregate in multicellular globules, thus a higher concentration could result in vascular embolization. One study suggested that  $5 \times 10^6$  cells as the maximum number of cells that could be safely transplanted [76]. Others concurred with this statement, where stem cell injections as high as  $5 \times 10^7$  cells caused high mortality rates due to embolisms [71]. Based on previous publications, it seems that a cell quantity of  $5 \times 10^6$  cells is an ideal cell quantity number [71]. Another study showed that animals died when they received greater than  $3 \times 10^7$  cells, stating  $1 \times 10^7$ – $2 \times 10^7$  cells might be the optimal range [77]. Reducing the number of cells would not be effective since a lower number of cells would not be enough to enter the brain for effective treatment [65, 72, 73]. Besides the number of cells, others have proposed that cell size and velocity of injection are of equal importance [70]. Slower injection might diminish sludging and thereby allow higher cell doses [70].

In clinical trials, different cell doses have been used. Based on mean body mass, Bang et al. [78] proposed that  $1 \times 10^8$  cells/patient is the human dose equivalent to the dose used in rodent stroke models. They considered  $1 \times 10^5$ – $3 \times 10^6$  cells/rat as the effective dose used in rodents. Two other trials proposed different doses [73, 79]. Other studies have shown that the dose of stem cells and more particularly MSC at a dose between  $8 \times 10^5$  and  $4 \times 10^8$  administered intravenously or in the subarachnoid space improve the neurological function in 33.3% of patients with the acute phase of SCI while in the chronic phase of SCI did not result in a significant improvement of the outcomes [80]. The absence of improvement in the chronic SCI patient could be explained by the presence of glial scarring which physically blocks axon regeneration [81].

Researchers must carefully consider the potential risks and benefits of different dosing strategies to ensure safe and effective stem cell transplantation. Research is needed to determine the optimal dose for different conditions and types of stem cells (Table 1).

## Way of administration

Preclinical studies use mainly three different injection routes: IC, intra-arterial (IA), and IV. IC stem cell transplantation seems to be the most effective route and results in the highest number of cell deposits into the target area of the brain (Table 1). However, this is also the most invasive route and studies have shown that the stereotactic inoculation of cells can cause hemorrhage or injury (probably by needle insertion), fluid loading, neuronal cell deaths, reactive gliosis, and micro-calcification [77, 82].



Both intravascular routes can avoid unnecessary brain damage compared to the invasiveness of the IC procedure. IA administration route has been correlated with a decrease in infarct volumes, functional recovery, and a high number of surviving stem cells. IA injection, however, holds the risk of cerebral embolisms and reduction of blood flow when high doses of stem cells are infused [70, 82]. IV injection is the less-invasive, simplest, and practical route of administration, but has the disadvantage of dispersing cells throughout the body, resulting in fewer cells reaching the brain parenchyma because of entrapment in the lungs and other peripheral organs [70, 71, 82].

Lately, tissue engineering created a new perspective and shown a potential solution to the dismal poor administration and regenerative capabilities of neuronal systems in re-establishing axonal connections after injury of diseases.

Graphene scaffolds, three-dimensional graphene foam, and other biomaterials can serve as substrates for the culture and differentiation of NSCs. NSCs grown on these materials can be guided to differentiate into specific neural cell types, such as neurons and glial cells. This approach can be utilized to generate neural tissue for transplantation, potentially replacing damaged or lost cells in neurological disorders [83].

Graphene-based materials (layers of carbon atoms arranged in a two-dimensional honeycomb lattice) possess unique properties that can facilitate improved cellular interactions. For example, graphene's high surface area and electrical conductivity can enhance cell adhesion, proliferation, and differentiation. By providing a favorable environment for stem cells to grow and develop. Graphene scaffolds and foam can potentially support the regeneration of neural tissue.

Graphene's electrical properties also enable the integration of electrical stimulation into stem cell therapy for neurological disorders. Electrical signals applied through graphene-based scaffolds can promote neural cell differentiation, guide axonal growth, and enhance neural network formation. This electrical stimulation can potentially aid in the functional recovery of damaged neural circuits [84, 85].

It is important to note that the potential of graphene-based materials in neurological stem cell therapy offers exciting prospects for the advancement of progressive nanotechnology and generative stem cell therapy. There are still challenges to overcome. These include optimizing the biocompatibility, long-term stability, and integration of graphene materials with neural tissue. Further research and development are necessary to fully understand their interactions with cells and their long-term effects *in vivo* [83].

## Timing of stem cell administration

Several studies have compared different administration times. For example, the study of Komatsu et al. [86] delivered stem cells in 3 time periods from 7 days after middle cerebral artery occlusion (MCAo) until 28 days after MCAo. The stem cells injected at 7 days post-MCAo did significantly better than the cells transplanted at 28 days [86]. Administration at 4 weeks post-MCAo might thus be too late to be effective [87]. The study of Nam et al. [79] on the other hand, compared 1 h, 1 day, or 3 days post-MCAo injection. The 1 h post-MCAo transplanted group showed maximum neurological recovery, in both functional and structural ways [78].

Several other preclinical studies support the early administration of stem cells. It seems that 24 h is the most optimal administration time because this might go along with the time of opening of the BBB [70, 82, 88]. However, this early administration has some practical implications when implemented in a real clinic setting. The preparation of autologous stem cells needs time for production and expansion before administration which will delay the administration. During the acute phase of the neurological disability, patient stabilization is mandatory to reduce secondary brain damage. All these would not make the patient suitable for early administration. Pilot studies have shown that many patients undergo marked improvement or worsening in the first week after stroke or trauma [89, 90]. In both cases, early transplantation of stem cells would be unethical, and late transplantation could be inefficient [63]. The exact optimal timing remains to be defined.

## Preconditioning for improved stem cell survival after transplantation

Despite the significant advancements in stem cell therapy, various factors hinder the acceptance and survival of stem cells. Within hours of transplantation, a considerable number of donor cells die, which is attributed to pathological processes, including local immunological and inflammatory responses, loss of trophic factors, and reduced perfusion and nutrients due to local primary factors responsible for the initial ischemic insult [91]. The efficacy of stem cell transplantation depends on the number of cells retained and active at the graft site, although increasing the amount of cell engraftment may overcome massive cell death and washout. Still, transplanting a such large number of cells could induce aggregation, vascular embolism, and inflammation generated by graft cell death and hence jeopardize the potential beneficial effect [71, 76, 77]. Therefore, it is essential to reinforce donor cells to withstand the microenvironmental rigors of the infarcted site by optimizing cell engraftment without increasing complications [92]. Previous study has shown that priming cells before transplantation with cytokines to a state of “readiness” by stimulating their survival pathways can fortify cell engraftment, leading to enhanced survival and overcoming numerous problems during the post-engraftment period [93].

Tissue engineering such as graphene scaffolds and three-dimensional graphene foam hold great promise, further research and development are necessary to fully understand their interactions with cells and their long-term effects *in vivo*. However, these materials offer exciting prospects for the advancement of progressive nanotechnology and generative stem cell therapy [83–85].

Additionally, the age of the recipient is a crucial factor, with young patients expected to have a greater potential for neuroplasticity and anti-inflammatory effects. Most neurological disorders however are expected to increase with age. Still, other neurological disorders such as TBI and neonatal stroke occur primarily in a young population. The anti-inflammatory effect of stem cell therapy is thus reasonably expected to produce greater neurological rescue from inflammation induced in young brains compared to adults. This was observed in the rat model of TBI [94] as well as in the hypoxemic ischemic neonatal mice model [95].

## Conclusions

Stem cell therapy has shown promising results in treating various neurological disorders in animal models. This animal approach allows a better understanding of the mechanisms involved as well as a better comprehension of the healing processes after a neurological disorder. Still translating these results to human clinical trials requires a significant amount of research and well-designed studies. High-quality preclinical studies should address factors such as the optimal cell type, quantity of stem cells administered, way of administration, underlying co-morbidities, and timing of delivery. These factors can significantly impact the effectiveness of stem cell therapy and must be carefully controlled and tested in preclinical studies to ensure successful translation to clinical settings. Additionally, it is crucial to ensure that preclinical studies are large and well-designed to provide robust evidence for the safety and efficacy of stem cell therapy. Despite the challenges, stem cell therapy holds tremendous promise for the treatment of neurological disorders. With continued research well-designed studies and implementation of tissue engineering, we may one day be able to unlock the full potential of this groundbreaking technology.

## Abbreviations

ESCs: embryonic stem cells

IA: intra-arterial

IC: intracerebral

iPSCs: induced pluripotent stem cells

IV: intravenous

MCAo: middle cerebral artery occlusion

MSCs: adult mesenchymal stem cells

NSCs: neural stem cells

SCI: spinal cord injury

TBI: traumatic brain injury

## Declarations

### Author contributions

SHI: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation.

### Conflicts of interest

The author declares that he has no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

Not applicable.

### Availability of data and materials

Not applicable.

### Funding

Not applicable.

### Copyright

© The Author(s) 2023.

## References

1. Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. *Nature*. 2006;441:1094–6.
2. Chopp M, Li Y. Treatment of neural injury with marrow stromal cells. *Lancet Neurol*. 2002;1:92–100.
3. Savitz SI. Developing cellular therapies for stroke. *Stroke*. 2015;46:2026–31.
4. Smart N, Riley PR. The stem cell movement. *Circ Res*. 2008;102:1155–68.
5. Verma RS. Breaking dogma for future therapy using stem cell—Where we have reached? *Indian J Med Res*. 2016;143:129–31.
6. Baraniak PR, McDevitt TC. Stem cell paracrine actions and tissue regeneration. *Regen Med*. 2010;5:121–43.
7. Hung CW, Liou YJ, Lu SW, Tseng LM, Kao CL, Chen SJ, et al. Stem cell-based neuroprotective and neurorestorative strategies. *Int J Mol Sci*. 2010;11:2039–55.
8. Crisostomo PR, Wang M, Herring CM, Markel TA, Meldrum KK, Lillemoie KD, et al. Gender differences in injury induced mesenchymal stem cell apoptosis and VEGF, TNF, IL-6 expression: role of the 55 kDa TNF receptor (TNFR1). *J Mol Cell Cardiol*. 2007;42:142–9.

9. Markel TA, Crisostomo PR, Wang M, Herring CM, Meldrum DR. Activation of individual tumor necrosis factor receptors differentially affects stem cell growth factor and cytokine production. *Am J Physiol Gastrointest Liver Physiol*. 2007;293:G657–62.
10. Ul Hassan A, Hassan G, Rasool Z. Role of stem cells in treatment of neurological disorder. *Int J Health Sci*. 2009;3:227–33.
11. Yang CS, He D, Tan J. Co-culture with vascular endothelial progenitor cells: effects on proliferation and apoptosis of neural stem cells and vascular remodeling in rats with ischemia reperfusion injury. *Chin J Tissue Eng Res*. 2017;21:718–23. Chinese.
12. Johansson CB, Svensson M, Wallstedt L, Janson AM, Frisen J. Neural stem cells in the adult human brain. *Exp Cell Res*. 1999;253:733–6.
13. Ayuso-Sacido A, Moliterno JA, Kratovac S, Kapoor GS, O'Rourke DM, Holland EC, et al. Activated EGFR signaling increases proliferation, survival, and migration and blocks neuronal differentiation in post-natal neural stem cells. *J Neurooncol*. 2010;97:323–37.
14. Pincus DW, Keyoung HM, Harrison-Restelli C, Goodman RR, Fraser RA, Edgar M, et al. Fibroblast growth factor-2/brain-derived neurotrophic factor-associated maturation of new neurons generated from adult human subependymal cells. *Ann Neurol*. 1998;43:576–85.
15. Arnhold S, Lenartz D, Kruttwig K, Klinz FJ, Kolossov E, Hescheler J, et al. GFP labelled ES cell derived neural precursor cells differentiate into Thy-1 positive neurons and glia after transplantation into the striatum of the adult rat striatum. *J Neurosurg*. 2000;93:1026–32.
16. Nasonkin I, Mahairaki V, Xu L, Hatfield G, Cummings BJ, Eberhart C, et al. Long-term, stable differentiation of human embryonic stem cell-derived neural precursors grafted into the adult mammalian neostriatum. *Stem Cells*. 2009;27:2414–26.
17. Zhang YW, Denham J, Thies RS. Oligodendrocyte progenitor cells derived from human embryonic stem cells express neurotrophic factors. *Stem Cells Dev*. 2006;15:943–52.
18. Michelsen KA, Acosta-Verdugo S, Benoit-Marand M, Espuny-Camacho I, Gaspard N, Saha B, et al. Area-specific reestablishment of damaged circuits in the adult cerebral cortex by cortical neurons derived from mouse embryonic stem cells. *Neuron*. 2015;85:982–97.
19. Liu Y, Weick JP, Liu H, Krencik R, Zhang X, Ma L, et al. Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. *Nat Biotechnol*. 2013;31:440–7.
20. Qu Z, Guan Y, Cui L, Song J, Gu J, Zhao H, et al. Transplantation of rat embryonic stem cell-derived retinal progenitor cells preserves the retinal structure and function in rat retinal degeneration. *Stem Cell Res Ther*. 2015;6:219.
21. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126:663–76.
22. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science*. 2007;318:1917–20.
23. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007;131:861–72.
24. Chun YS, Chaudhari P, Jang YY. Applications of patient-specific induced pluripotent stem cells; focused on disease modeling, drug screening and therapeutic potentials for liver disease. *Int J Biol Sci*. 2010;6:796–805.
25. Peng Y, Zhao Z. Application of human induced pluripotent stem cells-derived dopaminergic neurons in the Parkinson's disease models: present and future. *Chin J Tissue Eng Res*. 2016;20:5458–65. Chinese.
26. Israel MA, Yuan SH, Bardy C, Reyna SM, Mu Y, Herrera C, et al. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature*. 2012;482:216–20.

27. Gamm DM, Phillips MJ, Singh R. Modeling retinal degenerative diseases with human iPS-derived cells: current status and future implications. *Exp Rev Ophthalmol*. 2013;8:213–6.
28. Tropepe V, Coles BL, Chiasson BJ, Horsford DJ, Elia AJ, McInnes RR, et al. Retinal stem cells in the adult mammalian eye. *Science*. 2000;287:2032–6.
29. Qin J, Song B, Zhang H, Wang Y, Wang N, Ji Y, et al. Transplantation of human neuro-epithelial-like stem cells derived from induced pluripotent stem cells improves neurological function in rats with experimental intracerebral hemorrhage. *Neurosci Lett*. 2013;548:95–100.
30. Du H, Lim SL, Grob S, Zhang K. Induced pluripotent stem cell therapies for geographic atrophy of age-related macular degeneration. *Semin Ophthalmol*. 2011;26:216–24.
31. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation*. 1968;6:230–47.
32. Choi YS, Dusting GJ, Stubbs S, Arunothayaraj S, Han XL, Collas P, et al. Differentiation of human adipose-derived stem cells into beating cardiomyocytes. *J Cell Mol Med*. 2010;14:878–89.
33. Kim KS, Kim HS, Park JM, Kim HW, Park MK, Lee HS, et al. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer’s disease model. *Neurobiol Aging*. 2013;34:2408–20.
34. Bernardo ME, Fibbe WE. Mesenchymal stromal cells: sensors and switchers of inflammation. *Cell Stem Cell*. 2013;13:392–402.
35. Bae JS, Jin HK, Lee JK, Richardson JC, Carter JE. Bone marrow-derived mesenchymal stem cells contribute to the reduction of amyloid-beta deposits and the improvement of synaptic transmission in a mouse model of pre-dementia Alzheimer’s disease. *Curr Alzheimer Res*. 2013;10:524–31.
36. Venkataramana NK, Kumar SK, Balaraju S, Radhakrishnan RC, Bansal A, Dixit A, et al. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson’s disease. *Transl Res*. 2010;155:62–70.
37. Aleynik A, Gernavage KM, Mourad YSH, Sherman LS, Liu K, Gubenko YA, et al. Stem cell delivery of therapies for brain disorders. *Clin Transl Med*. 2014;3:24.
38. Karussis D, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol*. 2010;67:1187–94.
39. Liu L, Eckert MA, Riazifar H, Kang DK, Agalliu D, Zhao W. From blood to the brain: Can systemically transplanted mesenchymal stem cells cross the blood-brain barrier? *Stem Cells Int*. 2013;2013:435093.
40. Sanberg PR, Eve DJ, Metcalf C, Borlongan CV. Advantages and challenges of alternative sources of adult-derived stem cells for brain repair in stroke. *Prog Brain Res*. 2012;201:99–117.
41. Park HJ, Lee PH, Bang OY, Lee G, Ahn YH. Mesenchymal stem cells therapy exerts neuroprotection in a progressive animal model of Parkinson’s disease. *J Neurochem*. 2008;107:141–51.
42. Peng J, Zeng X. The role of induced pluripotent stem cells in regenerative medicine: neurodegenerative diseases. *Stem Cell Res Ther*. 2011;2:32.
43. Thompson LH, Björklund A. Reconstruction of brain circuitry by neural transplants generated from pluripotent stem cells. *Neurobiol Dis*. 2015;79:28–40.
44. Yasuhara T, Matsukawa N, Hara K, Yu G, Xu L, Maki M, et al. Transplantation of human neural stem cells exerts neuroprotection in a rat model of Parkinson’s disease. *J Neurosci*. 2006;26:12497–511.
45. Mu S, Wang J, Zhou G, Peng W, He Z, Zhao Z, et al. Transplantation of induced pluripotent stem cells improves functional recovery in Huntington’s disease rat model. *PLoS One*. 2014;9:e101185.
46. Ju R, Wen Y, Gou R, Wang Y, Xu Q. The experimental therapy on brain ischemia by improvement of local angiogenesis with tissue engineering in the mouse. *Cell Transplant*. 2014;23:83–95.
47. Ghazale H, Ramadan N, Mantash S, Zibara K, El-Sitt S, Darwish H, et al. Docosahexaenoic acid (DHA) enhances the therapeutic potential of neonatal neural stem cell transplantation post-traumatic brain injury. *Behav Brain Res*. 2018;340:1–13.

48. Nicaise C, Mitrecic D, Falnkar A, Lepore AC. Transplantation of stem cell-derived astrocytes for the treatment of amyotrophic lateral sclerosis and spinal cord injury. *World J Stem Cells*. 2015;7:380–98.
49. Riordan NH, Morales I, Fernandez G, Allen N, Fearnot NE, Leckrone ME, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. *J Transl Med*. 2018;16:57.
50. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. 2016;15:455–532.
51. Xia Y, Zhu J, Yang R, Wang H, Li Y, Fu C. Mesenchymal stem cells in the treatment of spinal cord injury: mechanisms, current advances and future challenges. *Front Immunol*. 2023;14:1141601.
52. Jiang Y, Zhang MJ, Hu BY. Specification of functional neurons and glia from human pluripotent stem cells. *Protein Cell*. 2012;3:818–25.
53. Chiou SH, Jiang BH, Yu YL, Chou SJ, Tsai PH, Chang WC, et al. Poly(ADP-ribose) polymerase 1 regulates nuclear reprogramming and promotes iPSC generation without c-Myc. *J Exp Med*. 2013;210:85–98.
54. Okano H, Nakamura M, Yoshida K, Okada Y, Tsuji O, Nori S, et al. Steps toward safe cell therapy using induced pluripotent stem cells. *Circ Res*. 2013;112:523–33.
55. Tan HK, Toh CXD, Ma D, Yang B, Liu TM, Lu J, et al. Human finger-prick induced pluripotent stem cells facilitate the development of stem cell banking. *Stem Cells Transl Med*. 2014;3:586–98.
56. Bedi SS, Hetz R, Thomas C, Smith P, Olsen AB, Williams S, et al. Intravenous multipotent adult progenitor cell therapy attenuates activated microglial/macrophage response and improves spatial learning after traumatic brain injury. *Stem Cells Transl Med*. 2013;2:953–60.
57. Corti S, Nizzardo M, Nardini M, Donadoni C, Salani S, Simone C, et al. Systemic transplantation of c-kit<sup>+</sup> cells exert a therapeutic effect in a model of amyotrophic lateral sclerosis. *Hum Mol Genet*. 2010;19:3782–96.
58. Sareen D, Ebert AD, Heins BM, Mcgovern JV, Ornelas L, Svendsen CN. Inhibition of apoptosis blocks human motor neuron cell death in a stem cell model of spinal muscular atrophy. *PLoS One*. 2012;7:e39113.
59. Freije JM, López-Otín C. Reprogramming aging and progeria. *Curr Opin Cell Biol*. 2012;24:757–64.
60. Miller JD, Ganat YM, Kishinevsky S, Bowman RL, Liu B, Tu EY, et al. Human iPSC-based modeling of late-onset disease via progerin-induced aging. *Cell Stem Cell*. 2013;13:691–705.
61. Glenn JD, Whartenby KA. Mesenchymal stem cells: emerging mechanisms of immunomodulation and therapy. *World J Stem Cells*. 2014;6:526–39.
62. Hausmann ON. Post-traumatic inflammation following spinal cord injury. *Spinal Cord*. 2003;41:369–78.
63. Meyer JD, Pryck JD, Hachimi-Idrissi S. Stem cell therapy for ischemic stroke: from bench to bedside. *Int J Crit Care Emerg Med*. 2018;4:058.
64. Sarveazad A, Toloui A, Moarrefzadeh A, Nafchi HG, Neishaboori AM, Yousefifard M. Mesenchymal stem cell-conditioned medium promotes functional recovery following spinal cord injury: a systematic review and meta-analysis. *Spine Surg Relat Res*. 2022;6:433–42.
65. Vu Q, Xie K, Eckert M, Zhao W, Cramer SC. Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke. *Neurology*. 2014;82:1277–86.
66. Stem cell therapies as an emerging paradigm in stroke participants. *Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS): bridging basic and clinical science for cellular and neurogenic factor therapy in treating stroke*. *Stroke*. 2009;40:510–5.
67. Savitz SI, Cramer SC, Wechsler L. Stem cells as an emerging paradigm in stroke 3: enhancing the development of clinical trials. *Stroke*. 2014;45:634–9.
68. Herberts CA, Kwa MSG, Hermsen HPH. Risk factors in the development of stem cell therapy. *J Transl Med*. 2011;9:29.

69. Liu XL, Zhang W, Tang SJ. Intracranial transplantation of human adipose-derived stem cells promotes the expression of neurotrophic factors and nerve repair in rats of cerebral ischemia-reperfusion injury. *Int J Clin Exp Pathol*. 2014;7:174–83.
70. Yavagal DR, Lin B, Raval AP, Garza PS, Dong C, Zhao W, et al. Efficacy and dose-dependent safety of intra-arterial delivery of mesenchymal stem cells in a rodent stroke model. *PLoS One*. 2014;9:e93735.
71. Yang Z, Cai X, Xu A, Xu F, Liang Q. Bone marrow stromal cell transplantation through tail vein injection promotes angiogenesis and vascular endothelial growth factor expression in cerebral infarct area in rats. *Cytotherapy*. 2015;17:1200–12.
72. Yang B, Migliati E, Parsha K, Schaar K, Xi X, Aronowski J, et al. Intra-arterial delivery is not superior to intravenous delivery of autologous bone marrow mononuclear cells in acute ischemic stroke. *Stroke*. 2013;44:3463–72.
73. Lim JY, Jeong CH, Jun JA, Kim SM, Ryu CH, Hou Y, et al. Therapeutic effects of human umbilical cord blood-derived mesenchymal stem cells after intrathecal administration by lumbar puncture in a rat model of cerebral ischemia. *Stem Cell Res Ther*. 2011;2:38.
74. Kranz A, Wagner DC, Kamprad M, Scholz M, Schmidt UR, Nitzsche F, et al. Transplantation of placenta-derived mesenchymal stromal cells upon experimental stroke in rats. *Brain Res*. 2010;1315:128–36.
75. Omori Y, Honmou O, Harada K, Suzuki J, Houkin K, Kocsis JD, et al. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats. *Brain Res*. 2008;1236:30–8.
76. Karlupia N, Manley NC, Prasad K, Schäfer R, Steinberg GK. Intraarterial transplantation of human umbilical cord blood mononuclear cells is more efficacious and safer compared with umbilical cord mesenchymal stromal cells in a rodent stroke model. *Stem Cell Res Ther*. 2014;5:45.
77. Liu YP, Seçkin H, Izcı Y, Du ZW, Yan YP, Başkaya MK. Neuroprotective effects of mesenchymal stem cells derived from human embryonic stem cells in transient focal cerebral ischemia in rats. *J Cereb Blood Flow Metab*. 2009;29:780–91.
78. Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. *Ann Neurol*. 2005;57:874–82.
79. Nam HS, Kwon I, Lee BH, Kim H, Kim J, An S, et al. Effects of mesenchymal stem cell treatment on the expression of matrix metalloproteinases and angiogenesis during ischemic stroke recovery. *PLoS One*. 2015;10:e0144218.
80. Yoon SH, Shim YS, Park YH, Chung JK, Nam JH, Kim MO, et al. Complete spinal cord injury treatment using autologous bone marrow cell transplantation and bone marrow stimulation with granulocyte macrophage-colony stimulating factor: phase I/II clinical trial. *Stem Cells*. 2007;25:2066–73.
81. Oh SK, Jeon SR. Current concept of stem cell therapy for spinal cord injury: a review. *Korean J Neurotrauma*. 2016;12:40–6.
82. Toyoshima A, Yasuhara T, Kameda M, Morimoto J, Takeuchi H, Wang F, et al. Intra-arterial transplantation of allogeneic mesenchymal stem cells mounts neuroprotective effects in a transient ischemic stroke model in rats: analyses of therapeutic time window and its mechanisms. *PLoS One*. 2015;10:e0127302.
83. Lazăr AI, Aghasoleimani K, Semertsidou A, Vyas J, Roşca AL, Ficaı D, et al. Graphene-related nanomaterials for biomedical applications. *Nanomaterials (Basel)*. 2023;13:1092.
84. Guo R, Xiao M, Zhao W, Zhou S, Hu Y, Liao M, et al. 2D Ti<sub>3</sub>C<sub>2</sub>T<sub>x</sub>MXene couples electrical stimulation to promote proliferation and neural differentiation of neural stem cells. *Acta Biomater*. 2022;139:105–17.

85. Saadati M, Akhavan O, Fazli H, Nemati S, Baharvand H. Controlled differentiation of human neural progenitor cells on molybdenum disulfide/graphene oxide heterojunction scaffolds by photostimulation. *ACS Appl Mater Interfaces*. 2023;15:3713–30.
86. Komatsu K, Honmou O, Suzuki J, Houkin K, Hamada H, Kocsis JD. Therapeutic time window of mesenchymal stem cells derived from bone marrow after cerebral ischemia. *Brain Res*. 2010;1334:84–92.
87. Stroemer P, Patel S, Hope A, Oliveira C, Pollock K, Sinden J. The neural stem cell line CTX0E03 promotes behavioral recovery and endogenous neurogenesis after experimental stroke in a dose-dependent fashion. *Neurorehabil Neural Repair*. 2009;23:895–909.
88. Dai J, Li SQ, Qiu YM, Xiong WH, Yin YH, Jia F, et al. Migration of neural stem cells to ischemic brain regions in ischemic stroke in rats. *Neurosci Lett*. 2013;552:124–8.
89. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells*. 2010;28:1099–106.
90. Tian C, Wang X, Wang X, Wang L, Wang X, Wu S, et al. Autologous bone marrow mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. *Exp Clin Transplant*. 2013;11:176–81.
91. Haider HK. Bone marrow cell therapy and cardiac reparability: better cell characterization will enhance clinical success. *Regen Med*. 2018;13:457–75.
92. Haider HK, Ashraf M. Preconditioning and stem cell survival. *J Cardiovasc Trans Res*. 2010;3:89–102.
93. Tabeshmehr P, Haider HK, Salmannejad M, Sani M, Hosseini SM, Khorraminejad Shiraz MH. Nicorandil potentiates sodium butyrate induced preconditioning of neurons and enhances their survival upon subsequent treatment with H<sub>2</sub>O<sub>2</sub>. *Transl Neurodegener*. 2017;6:29.
94. Dewan S, Schimmel S, Borlongan CV. Treating childhood traumatic brain injury with autologous stem cell therapy. *Expert Opin Biol Ther*. 2018;18:515–24.
95. Miller JT, Bartley JH, Wimborne HJ, Walker AL, Hess DC, Hill WD, et al. The neuroblast and angioblast chemotactic factor SDF-1 (CXCL12) expression is briefly up regulated by reactive astrocytes in brain following neonatal hypoxic-ischemic injury. *BMC Neurosci*. 2005;6:63.
96. Holley SM, Kamdjou T, Reidling JC, Fury B, Coleal-Bergum D, Bauer G, et al. Therapeutic effects of stem cells in rodent models of Huntington's disease: review and electrophysiological findings. *CNS Neurosci Ther*. 2018;24:329–42.
97. Zheng W, ZhuGe Q, Zhong M, Chen G, Shao B, Wang H, et al. Neurogenesis in adult human brain after traumatic brain injury. *J Neurotrauma*. 2013;30:1872–80.
98. Glass JD, Hertzberg VS, Boulis NM, Riley J, Federici T, Polak M, et al. Transplantation of spinal cord-derived neural stem cells for ALS: analysis of phase 1 and 2 trials. *Neurology*. 2016;87:392–400.
99. Zhou Z, Shi B, Xu Y, Zhang J, Zhou X, Feng B, et al. Neural stem/progenitor cell therapy for Alzheimer disease in preclinical rodent models: a systematic review and meta-analysis. *Stem Cell Res Ther*. 2023;14:3.
100. Chen ZZ, Niu YY. Stem cell therapy for Parkinson's disease using non-human primate models. *Zool Res*. 2019;40:349–57.
101. Wang Q, Matsumoto Y, Shindo T, Miyake K, Shindo A, Kawanishi M, et al. Neural stem cells transplantation in cortex in a mouse model of Alzheimer's disease. *J Med Invest*. 2006;53:61–9.
102. Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, Soldner F, et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *Proc Natl Acad Sci U S A*. 2008;105:5856–61.



103. Jeon I, Lee N, Li JY, Park IH, Park KS, Moon J, et al. Neuronal properties, *in vivo* effects, and pathology of a Huntington's disease patient-derived induced pluripotent stem cells. *Stem Cells*. 2012;30:2054–62.
104. Kaye JA, Finkbeiner S. Modeling Huntington's disease with induced pluripotent stem cells. *Mol Cell Neurosci*. 2013;56:50–64.
105. Park H, Chang KA. Therapeutic potential of repeated intravenous transplantation of human adipose-derived stem cells in subchronic MPTP-induced Parkinson's disease mouse model. *Int J Mol Sci*. 2020;21:8129.
106. Tajiri N, Acosta SA, Shahaduzzaman M, Ishikawa H, Shinozuka K, Pabon M, et al. Intravenous transplants of human adipose-derived stem cell protect the brain from traumatic brain injury-induced neurodegeneration and motor and cognitive impairments: cell graft biodistribution and soluble factors in young and aged rats. *J Neurosci*. 2014;34:313–26.
107. Zhao CP, Zhang C, Zhou SN, Xie YM, Wang YH, Huang H, et al. Human mesenchymal stromal cells ameliorate the phenotype of SOD1-G93A ALS mice. *Cytherapy*. 2007;9:414–26.
108. Shroff G. A review on stem cell therapy for multiple sclerosis: special focus on human embryonic stem cells. *Stem Cells Cloning*. 2018;12;11:1–11.