

Potential Significance of Neural Stem Cell-Based Therapy for Future Clinical Practice

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ABSTRACT

Introduction: Disorders of the central nervous system contribute to long-term disabilities. Current treatments have not been able to fully replace the damaged tissue and dysfunctional neurons. Treatment options aiming at driving both structural and functional repair of neuronal tissue such as neural stem cells therapy has attracted many researcher. This narrative review aims to examine the therapeutic potential of neural stem cells and highlights some of the challenges in harnessing NSCs use into clinical practice.

Methods: Two database including Pubmed and Scopus were used for literature search. Relevant studies were included in the review.

Results: Both exogenous stem cell transplantation and endogenous neurogenesis seem to show potential for the treatment of several neurological disorders. However, several challenges remain with regards to the translation of neural stem cells therapy into clinical practice.

Conclusion: Neural stem cell-based therapy provides great potential for future clinical practice. However, further research is required to ensure the clinical efficacy and efficiency in delivering the therapy.

Keywords: neurogenesis; neural stem cell; translational research; neurodegeneration; brain injury

INTRODUCTION

Diseases of the central nervous system (CNS) including traumatic injuries to the brain and spinal cord, stroke, and neurodegenerative diseases such as Alzheimer's and Parkinson's disease represent a leading cause of long-term disability and mortality worldwide¹. One of the main barriers to treating these conditions is the limited capacity for CNS regeneration following structural damage². Standard pharmacological therapy remain largely palliative aiming at symptom management without replacing lost neurons or restoring dysfunctional neuronal circuits. Consequently, therapeutic option capable of driving structural and functional repair of neuronal tissue including neural stem cells (NSCs) has emerged as one potential candidate for this effort².

Neural stem cells (NSCs) are a specialized type of stem cell found in the central nervous system. They are equipped with unique properties and significant potential for research and therapy. NSCs are progenitor cells with multipotent and self-renewing capacity^{3,4}. They are able to differentiate into the three principal cell types of the CNS: neurons, astrocytes, and oligodendrocytes⁴. Beyond their potential to physically replace dead or damaged cells, NSCs play a critical role in modifying disease condition through paracrine signaling. In clinical settings, both endogenous and transplanted NSCs secrete various

growth factors including neurotrophic, immunomodulatory, and pro-angiogenic factors that attenuate neuroinflammation, protect host tissue from secondary degeneration, and stimulate endogenous repair pathways (see Figure 1)⁵.

The potential role of neural stem cells in clinical treatment has been a great attraction for many researchers. Scientists believe that these cells have potential significance for future clinical practice for a variety of reasons including the fact that neurogenesis occurs in the adult human brain and plays an important role in learning and memory as well as mood regulation. Besides that, certain neural diseases can trigger neurogenesis in the injured site of brain⁶. However, the efficiency of neural stem cells-based therapy has not been proven and thus, further in-depth investigation to alleviate the drawbacks must be done.

Over centuries, there has been an antiquated view that the adult mammalian brain cannot create new neurons and is structurally constant. Many people believed that neurogenesis, a process of creating new neurons, only occurred during embryonic development and stops before puberty⁷. As a consequence, injured or damaged neurons, especially brain neurons in adults will lead to permanent loss of normal function. However, many studies reveal that neurogenesis does happen in adults. For example, previous studies reported that new neurons were added in the primate *dentate gyrus*, a structure located in hippocampus which is medial to the temporal lobe of human brain and plays a role in producing neural stem cells. Other studies showed evidence that the same phenomenon occurred in humans⁸. Later, new experiments were conducted to investigate the implication of adult neurogenesis and seek potential therapeutic methods by using this mechanism. Understanding the mechanisms of natural neurogenesis will help inform the design and interpretation of exogenous stem cell therapies for CNS diseases. This review aims to examine the potential role of neural stem cells in treatment of disorders of the CNS. Specifically, it highlights some of the challenges in harnessing NSCs use into clinical practice. Thus, it offers a novel translational synthesis which integrates mechanistic insights with CNS pathologies and practical clinical considerations.

METHOD

A comprehensive literature search was conducted to identify relevant studies investigating neural stem cell therapy, neurogenesis and their therapeutic potential for diseases of the central nervous system. The electronic databases PubMed and Scopus were used for study search. The search strategy utilized a combination keywords: (neural stem cell OR neurogenesis) AND (brain injury OR stroke OR neurodegeneration OR neurodegenerative disease). The search was limited to articles published in English. Relevant studies were reviewed and included in the study. Studies conducted both in animals and human were included. Studies published in the last ten years (2016 – 2026) were the main focus, however, some older articles were included where relevant i.e. for original attribution purpose.

RESULT

Neurogenesis, learning and memory and mood regulation

It is thought that neurogenesis might influence learning and memory due to certain pieces of evidence. Firstly new neurons are added to structures such as hippocampus, midbrain, lateral prefrontal cortex, and posterior parietal cortex which are responsible for learning and memory function⁸. The frontal parietal cortex are responsible for short term memory. On the other hand, hippocampus, a structure located in the medial temporal lobe, and midbrain play a role in long term memory called episodic and semantic memory. Episodic memory is used to keep track of individual experience while semantic memory is needed to collect and store factual knowledge about the world. In addition to that, hippocampus is also required to remember places an individual has ever visited, how to get there and what events they have experienced. Secondly, a decreased number of new neurons impair the ability to

carry out the task which is dependent on hippocampus function^{9,10}. As previously mentioned, hippocampus is crucial in forming memories about places and events. One of the methods to test the function of this structure is The Moris task. Thirdly, increased production of hippocampal cells results in better performance in hippocampal-dependent learning tasks¹⁰. The number of new neurons has a positive correlation with learning. A study was conducted to evaluate the performance of mice during spatial navigation learning in the Moris task. The result showed that the mice with smallest number of new neurons performed badly during the task. Besides, an increased number of immature neurons has been proven to improve the performance on learning tasks which depend on the hippocampus function. Some factors including estrogen, environmental complexity and physical exercises are among factors which enhance the production of new neurons. Another study indicates that decreased number of neurons due to stress are associated with learning impairment. Some drugs such as opiates, nicotine, and alcohol are also correlated with decreased neurogenesis which lead to worse performance in some learning activities¹¹.

Some studies indicated the potential role of neurogenesis in regulating mood. Some conditions which cause chronic stress result in lower production of new neurons. On the other hand, some physical and chemical antidepressants indicate the reverse effect. These findings are an entry point for further investigation as to whether or not neurogenesis plays an important role in antidepressant function. Another study reported that environmental factors such as stress which induces depression in humans can lead to cell death and reduction of neurotrophins level. Besides, they also decrease hippocampal neurogenesis^{12,13,14}. It is not conclusive yet whether these events give rise to the pathogenesis of depression. However, the fact that neurogenesis in adult hippocampus is impaired by stress and enhanced by chronic antidepressant leads to a hypothesis that this process may take in the pathogenesis as well as treatment of mood disorder.

Further investigation was done to test whether hippocampal neurogenesis plays a role in the mechanism of action of antidepressant. X-ray irradiation was subjected to hippocampus to disrupt neurogenesis process. The study revealed that this treatment led to blockage of antidepressant effects. This finding supports the hypothesis that neurogenesis plays a role in the effect of antidepressants. However, the researcher cannot eliminate the possibility that other impacts of hippocampal irradiation also contribute to the decreased effect of antidepressant. Another study also reported the involvement of hippocampal neurogenesis in mood regulation which strengthened the belief that it has potential in treating depression and other mood disorders¹⁴. Overall, the finding suggest that enhancing endogenous neurogenesis may be beneficial in improving disease conditions related to cognitive impairment and mood regulation.

Neurogenesis and Injury of the CNS

In addition to the fact that neurogenesis contributes to the process of learning, memory as well as the regulation of mood, it also plays a role in the injured area of brain. Brain injury enhances the proliferation of surrounding neural stem cells which can promote the production of more neural cells⁷. A study in rodents shows that after an ischemic stroke, newborn cells are found at the site of injury. These are cells migrating from the subventricular zone. In human stroke patients, recruitment of newborn cells to the site of infarct might happen as well¹⁵. However, no one can explain how long these cells can survive. Whether these cells are able to differentiate to become mature neurons and integrate into the existing circuitry is still a mystery^{7,15}.

Neural stem cells, the precursor of neurons, are spread throughout the entire area of the brain. However, not all of the cells can differentiate into neurons. These cells are divided into three groups. The first one is those located in the subventricular zone, an area in the lateral ventricle of brain, and dentate gyrus which have the ability to generate neurogenesis automatically. This means that they can produce new neurons. The second group is cells located in subcallosal zone, an area near the

subventricular zone. Cells in this area mostly die before finishing the process of becoming mature neurons. This failure is commonly due to the lack of environmental support. The last group covers cells located in other areas of the brain which cannot induce neurogenesis spontaneously under normal conditions¹⁶.

The fact shows that spontaneous production of new neurons only happens in two areas of the brain: the subventricular zone and dentate gyrus. Many clinicians are curious whether these cells can migrate to the damaged site of the brain, for example due to stroke and replace the function of already dead neurons. Arvidsson et al. (2002) claim that new neurons are found in the damaged area after stroke attack. These cells migrate from their original site in subventricular zone or dentate gyrus to the area of injury and then proliferate. This migration is caused by signals transmitted from dead neurons. However, how these signaling chemicals work to recruit new neurons is not clear yet. The study showed that there were 6,300 of new neurons per mm³ in damaged area 14 days after a stroke¹⁷. More recently, quantitative studies in rodents also confirm that stroke induces a rapid endogenous neurogenesis peaking between 10 and 14 days post-infarct¹⁸. This indicates that the response neurogenesis is a crucial response to injury. However, further observation on the same research revealed that four weeks later, over three quarters of these cells died. It was suspected that these deaths was due to the unsuitable environment which could not support the development of these cells^{17,19}.

Arvidsson et al (2002) describes the mechanism of self-reparation of death brain neurons. Firstly, cell precursors for neurogenesis proliferate in their original sites and probably also in the local damaged area. These cells then migrate to the injured region and undergo a differentiation phase into mature neurons. Lastly, they must integrate with the existing neural circuits to be able to replace the function of death neurons. However, the fact that the number of new neurons which can survive in the new environment drops significantly forces the researcher to find new strategies to develop a more effective treatment for such disease.

Borlongan and Hess (2006) report that the neural stem cells can be used to improve the condition in stroke rats. In the study, a clone of the neural stem cell was transplanted in stroke rats and found that four weeks later, their motor and cognitive performance were better. Furthermore, this method was implemented in a clinical trial in which twelve stroke patients underwent cell transplantation. The result was satisfying and it strengthened the hypothesis that transplanting stem cells could be a good alternative for stroke treatment²⁰. To note, a recent systematic review of clinical trials suggest that stem cell therapy can promote recovery after ischemic stroke. It is reported that intracerebral delivery of stem cells provided better functional outcome as measured with standardized scales such as the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). However, despite the fact that this direct delivery is effective, it also carries higher risk to the patient due to the invasiveness of the procedure²¹.

Although stem cell transplantation seems to be quite promising, the implementation of this procedure can be impractical. The clinician must take into account the side effects of surgery, the likelihood of graft rejection, and uncontrollable grafted cell growth leading to tumor formation. In addition to that, the availability of the neural stem cell supply must be considered as well²⁰. The research on stem cell therapy for treating stroke conducted either clinically or experimentally has resulted in a great variety of outcomes. In addition to that, stroke models on animals may give a different result when applied to humans. However, he insists that stem cell transplantation is one of the potential treatments for stroke patients^{22,23}.

To overcome the drawbacks of the transplantation procedure, another approach that can be used is mobilization and amplification of the existing neural stem cells in the brain. Former studies have revealed that certain conditions such as ischemia can trigger neurogenesis. However, to abolish the deterioration and replace the function of already dead cells, this disease-induced neurogenesis seems to be insufficient. Therefore, researchers must perform additional intervention to realize complete repair

of the neuron. Investigators today are focusing on finding methods to boost disease-induced neurogenesis. Neurogenesis stimulating agents such as G-CSF and exercise have been proposed to help enhance endogenous neurogenesis²⁰. Several approaches to stimulate endogenous neurogenesis have been conducted. Those includes the administration of certain protein such as fibroblast growth factor-2 (FGF-2), epidermal growth factor (EGF), granulocyte colony-stimulating factor (G-CSF) and brain-derived neurotrophic factor (BDNF) and angiogenesis stimulating molecules²⁴.

Endogenous NSCs

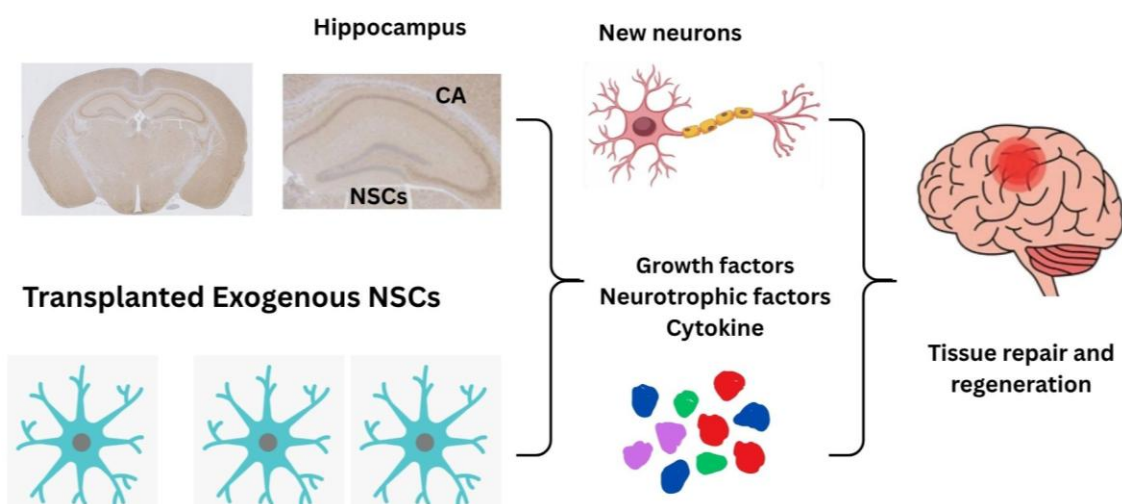


Figure 1. Neural stem cells from endogenous and exogenous source. Neural stem cells resides in the hippocampus and support adult neurogenesis. Exogenous cells are delivered through transplantation. Both mechanisms are thought to be involved in recovery to brain injuries. NSCs: neural stem cells. The brain coronal section image was the work of Bmouzon (source: https://commons.wikimedia.org/wiki/File:Sagital_Vs_Coronal.png)

DISCUSSION

There are several challenges that significantly hinder the effort in harnessing NSCs for therapeutic use in neurological disorders and injuries of the CNS. The translational application of NSC-based therapies into clinical practice is constrained by complex biological, safety, and methodological hurdles. Firstly, there is limited availability of NSCs source. Securing a sufficient and reliable source of adult NSCs is a primary challenge, as these cells are not easily accessible in large quantities from adult tissues. Until today, there has been ongoing issues and controversies regarding the best methods for deriving NSCs from various sources, including ethical concerns (i.e. the use of embryonic tissue) and technical limitations^{25,26}. Secondly, controlling lineage-specific differentiation and long-term fate of transplanted cells remains a major hurdle²⁷. Both unmodified and genetically modified NSCs may also pose potential hazards, such as unregulated cellular multiplication or inappropriate differentiation, which can prevent them from maturing into functional, signaling neurons. This in turn can elevate safety concerns regarding tumorigenicity, genomic instability, and ectopic tissue growth^{27,28}. Thirdly, there are problems with the survival of NSCs. Following transplantation, NSCs often exhibit poor survival, which limits their therapeutic effectiveness. Injured or damaged neural tissue often have hostile environment, thus maintaining stable proliferation and achieving targeted differentiation of NSCs into functional neurons can be a real challenge. The hostile microenvironment of damaged tissues of the central nervous system, often characterized by severe neuroinflammation, ischemia, and oxidative stress, substantially compromises graft survival, cell migration, and structural synaptic integration into

host neural circuits²⁹. The hostile microenvironment is often driven by secondary injury cascade whereby initial vascular disruption and blood-brain barrier breakdown leads to glutamate-induced excitotoxicity and the production of reactive oxygen species^{17, 29}. Moreover, transplantation of exogenous NSCs can trigger immune responses, which poses safety risks. Host immune rejection is a key barrier for allogeneic NSC therapies, whereas autologous or induced pluripotent stem cell alternatives present challenges related to line-to-line variability, donor epigenetic memory, and extended preparation timelines^{27,30}.

Apart from the biological complications, other factors may contribute to the lack of translation of NSC therapies from preclinical research into routine medical practice including bioprocessing, procedural, regulatory, and economic barriers. To scale up cell manufacturing while maintaining adherence to Good Manufacturing Practice standards requires standardized bioprocessing pipelines to maintain high cell purity, functional potency, and consistency from batch-to-batch^{29,30}. Direct delivery to precise neuroanatomical target sites demands specialized neurosurgical protocols to minimize surgical trauma, tissue disruption, and off-target dissemination²⁸. Additionally, non-invasive *in vivo* tracking of engrafted cells to monitor long-term survival, migration patterns, and biodistribution remains technically challenging without altering cellular viability²⁹. Many obstacles remain in translating preclinical findings to effective patient therapies, including defining appropriate patient populations and treatment protocols. The heterogeneity of patient, disease progression that can be unpredictable, a lack of prognostic biomarkers, rigid regulatory oversight, and high cost of manufacturing together complicates the translation into clinical trials^{7,30}. For example, a clinical trial of NSCs in chronic stroke patients revealed variations in response among the participants i.e. improved upper limb function was not seen in patients with absent upper limb movement at baseline which suggests a possible target population for future clinical trials³¹.

CONCLUSION

Based on the research findings above, it is clear that neural stem cell-based therapy provides great potential for future clinical practice. This hypothesis is based on the evidence that neurogenesis does occur in humans and it also exists in the site of injured brain. Having been proven to play a role in several brain functions, it may contribute to the development of new therapy. However, studies showed that the proposed treatments still have several drawbacks. Thus, further research is needed to find the most effective method.

CONFLICT OF INTEREST

The author declares no conflict of interest

REFERENCES

1. Raj R, Kaprio J, Korja M, Mikkonen ED, Jousilahti P, Siironen J. Risk of hospitalization with neurodegenerative disease after moderate-to-severe traumatic brain injury in the working-age population: a retrospective cohort study using the Finnish national health registries. *PLoS medicine*. 2017 Jul 5;14(7):e1002316.
2. Gögel S, Gubernator M, Minger SL. Progress and prospects: stem cells and neurological diseases. *Gene therapy*. 2011 Jan;18(1):1-6.
3. Lee Y, Boschian C, Ko K. MicroRNA-mediated regulation of proliferation, lineage differentiation, and apoptosis in neural stem cells. *RNA biology*. 2025 Dec 31;22(1):1-7.

4. Horie N. Neural Stem Cells/Neuronal Progenitor Cells. Cell Therapy Against Cerebral Stroke: Comprehensive Reviews for Translational Researches and Clinical Trials. 2017 Jan 7:27-37.
5. Huang J, Cai H, Zhu Z, Zhang G, Zhang Y, Li R, et al. Exosomes derived from neural stem cells regulates neural stem cells and applicates in nervous system diseases. Chinese Journal of Neuromedicine. 2023:826-32.
6. Leung JW, Cheung KK, Ngai SP, Tsang HW, Lau BW. Protective effects of melatonin on neurogenesis impairment in neurological disorders and its relevant molecular mechanisms. International journal of molecular sciences. 2020 Aug 6;21(16):5645.
7. Kim HJ, Sun W. Adult neurogenesis in the central and peripheral nervous systems. International Neurology Journal. 2012 Jun 30;16(2):57.
8. Abbott LC, Nigussie F. Adult neurogenesis in the mammalian dentate gyrus. Anatomia, histologia, embryologia. 2020 Jan;49(1):3-16.
9. Evans A, Terstege DJ, Scott GA, Tsutsui M, Epp JR. Neurogenesis mediated plasticity is associated with reduced neuronal activity in CA1 during context fear memory retrieval. Scientific Reports. 2022 Apr 29;12(1):7016.
10. Cope EC, Gould E. Adult neurogenesis in the hippocampus: A role in learning and memory. In The Curated Reference Collection in Neuroscience and Biobehavioral Psychology 2016 Jan 1 (pp. 345-358). Elsevier Science Ltd..
11. Leuner B, Gould E, Shors TJ. Is there a link between adult neurogenesis and learning?. Hippocampus. 2006;16(3):216-24.
12. Siteneski A, Olescowicz G, Pazini FL, Camargo A, Fraga DB, Brocardo PS, Gil-Mohapel J, Cunha MP, Rodrigues AL. Antidepressant-like and pro-neurogenic effects of physical exercise: the putative role of FNDC5/irisin pathway. Journal of neural transmission. 2020 Mar;127(3):355-70.
13. Bhagya VR, Srikumar BN, Veena J, Shankaranarayana Rao BS. Short-term exposure to enriched environment rescues chronic stress-induced impaired hippocampal synaptic plasticity, anxiety, and memory deficits. Journal of Neuroscience Research. 2017 Aug;95(8):1602-10.
14. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. science. 2003 Aug 8;301(5634):805-9.
15. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. Cell. 2008 Feb 22;132(4):645-60.
16. Kim JY, Shaker MR, Lee JH, Lee B, Kim H, Sun W. Identification of molecular markers distinguishing adult neural stem cells in the subventricular and subcallosal zones. Animal cells and systems. 2017 May 17;21(3):152-9.
17. Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nature medicine. 2002 Sep;8(9):963-70.
18. Cuartero MI, García-Culebras A, Torres López C, Moro MA. Post-stroke neurogenesis: friend or foe? Front Cell Dev Biol. 2021 Mar 22;9:657846.
19. Ceanga M, Dahab M, Witte OW, Keiner S. Adult neurogenesis and stroke: a tale of two neurogenic niches. Front Neurosci. 2021; 15: 700297

20. Borlongan CV, Hess DC. New hope for stroke patients: mobilization of endogenous stem cells. *Canadian Medical Association Journal*. 2006 Mar 28;174(7):954-5.
21. Fauzi AA, Thamrin AM, Permana AT, Ranuh IA, Hidayati HB, Hamdan M, Wahyuhadi J, Suroto NS, Lestari P, Chandra PS. Comparison of the administration route of stem cell therapy for ischemic stroke: a systematic review and meta-analysis of the clinical outcomes and safety. *Journal of Clinical Medicine*. 2023 Apr 6;12(7):2735.
22. Li W, Shi L, Hu B, Hong Y, Zhang H, Li X, Zhang Y. Mesenchymal stem cell-based therapy for stroke: current understanding and challenges. *Frontiers in Cellular Neuroscience*. 2021 Feb 9;15:628940.
23. Lalu MM, Montroy J, Dowlatshahi D, Hutton B, Juneau P, Wesch N, Y. Zhang S, McGinn R, Corbett D, Stewart DJ, A. Fergusson D. From the lab to patients: a systematic review and meta-analysis of mesenchymal stem cell therapy for stroke. *Translational stroke research*. 2020 Jun;11(3):345-64.
24. Zhao LR, Willing A. Enhancing endogenous capacity to repair a stroke-damaged brain: An evolving field for stroke research. *Progress in neurobiology*. 2018 Apr 1;163:5-26.
25. Luo Z, Shangguan Z, Cao L, Zhang Y, Li Q, Shi X, Fu J, Wang C, Dou X, Tan W, Li Q. Cerebrospinal fluid-contacting neurons: a promising source for adult neural stem cell transplantation in spinal cord injury treatment. *Frontiers in Cell and Developmental Biology*. 2025 Mar 12;13:1549194.
26. Tang Y, Yu P, Cheng L. Current progress in the derivation and therapeutic application of neural stem cells. *Cell death & disease*. 2017 Oct;8(10):e3108-.
27. Shah AJ, Dar MY. Jan B, et al. Neural Stem Cell Therapy for Alzheimer's Disease: A-State-of-the-Art Review. *Journal of Dementia and Alzheimer's Disease*. 2024;1(2), 109-25.
28. Master Z, McLeod M, & Mendez I. Benefits, risks and ethical considerations in translation of stem cell research to clinical applications in Parkinson's disease. *Journal of Medical Ethics*. 2007;33(3): 69–173.
29. Wei L, Yan W, Shah, W, et al. Advancements and challenges in stem cell transplantation for regenerative medicine. *Heliyon*. 2024;10(16):e35836.
30. Brianna APK, Wong YP. Applying stem cell therapy in intractable diseases: a narrative review of decades of progress and challenges. *Stem Cell Investig*. 2022;9:4
31. Muir KW, Bulters D, Willmot M, Sprigg N, Dixit A, Ward N, et al. Intracerebral implantation of human neural stem cells and motor recovery after stroke: multicentre prospective single-arm study (PISCES-2). *J Neurol Neurosurg Psychiatry*. 2020 Aug;91(8):855-862.