SciMedCentral

JSM Biotechnology & Biomedical Engineering

Review Article

Review of Clinical Trials Using Neural Stem Cells

Kristell Barreau[1#], Claire Lépinoux-Chambaud[1,2#], and Joël Eyer[1*]

[1]*Laboratoire Neurobiologie and Transgenese, Institut de Biologie en Santé, France*
[2]*Laboratoire Neurobiologie and Transgenese, Université d'Angers, France*
[#]*Both authors are co-first authors*

***Corresponding author**
Eyer Joël, Laboratoire de Neurobiologie and Transgenese, L'UNAM, UPRES EA-3143, Institut de Biologie en Santé, Université d'Angers, Centre Hospitalier Universitaire, Bâtiment IBS-IRIS, 49033 Angers, France, Tel: 02 44 68 84 88; E-mail: joel.eyer@univ-angers.fr

Submitted: 11 June 2016
Accepted: 27 July 2016
Published: 28 July 2016
ISSN: 2333-7117

Copyright
© 2016 Eyer et al.

OPEN ACCESS

Keywords
- Brain disorders
- Brain tumours
- Clinical trials
- Neural stem cells
- Neurodegenerative diseases
- Stem cells

Abstract

The use of stem cells in clinical trials started several years ago for regenerative-based therapies or for the treatment of tumours. After brain injuries or neurodegenerative diseases, neural stem cells represent a promising strategy to repair the affected tissue and to replace degenerative cells. Neural stem cells can migrate and differentiate into neurons, astrocytes and oligodendrocytes, and thus could serve as promising therapeutic solutions. However, these cells can represent a potential source of cancer stem cells in tumour brain where they are responsible of recurrence, invasiveness and resistance to current treatments. Thus, few clinical trials involving endogenous, genetically modified- or derived-neural stem cells have been conducted in the world to treat brain disorders. According to the website www.clinicaltrials.gov only 37 clinical trials involving neural stem cells are listed. Most of them use derived-neural stem cells to treat brain disorders (neurodegenerative diseases, injuries or tumours). For the future, a better approach would be to target directly endogenous stem cells.

ABBREVIATIONS

ALS: Amyotrophic Lateral Sclerosis; G-SCF: Granulocyte-colony Stimulating Factor; HSSC: Human Spinal cord derived-Stem Cell; HuCNS-Sc: Human Central Nervous System Derived-Stem Cell; INCL: Infantil Neuronal Ceroid Lipofuscinosis; iPSC: Induced-Pluripotent Stem Cell; MRI: Magnetic Resonance Imaging; NSC: Neural Stem Cell

INTRODUCTION

Stem cells are located in a lot of tissues or organs, including blood [1], teeth [2], bone marrow [3], brain [4] and human umbilical cord blood [5]. Their main properties are to divide, renew themselves and differentiate in specialized cells types.

Currently, 5508 clinical trials using stem cells are listed on the website www.clinicaltrials.gov, of which 320 studies are in phase 3 or 4 in many diseases including bacterial and fungal, central nervous system, lung, digestive diseases or cancer. Hematopoietic stem cells from peripheral blood or bone marrow are the most used, followed by mesenchymal stem cells. Neural stem cells (NSCs) represent an important source of stem cells from brain that can differentiate into neurons, oligodendrocytes or astrocytes, and they are responsible of neurogenesis in human adult brain. Moreover, several studies showed their ability to migrate to a lesion area following brain injuries, such as neurodegenerative diseases (Alzheimer, Parkinson), strokes, or brain tumours [6,7]. Unfortunately, it seems that this capacity is too low to repair efficiently the injured tissue because no self-rescue has been shown yet in patients. These cells also represent a source for cancer stem cells, which are responsible of the tumour recurrence as they resist to current treatments [8]. Manipulating endogenous and genetically modified NSCs have been used in several studies to treat neurodegenerative disorders, spinal cord lesions, and malignant glioma [9,10]. These cells represent promising and innovative resource for anti-tumour and regenerative-based therapies in order to repair damaged brain. Here, we will review the completed or ongoing clinical trials using NSCs across the world and will describe some results of these clinical trials.

LISTING OF ALL CLINICAL TRIALS USING NEURAL STEM CELLS

Currently, there are 37 clinical trials involving NSCs in the world (Figure 1A). All of them are listed in tables 1 and 2.According to ClinicalTrials.gov, the first clinical use of NSCs started in 2006 at the Peking University, China, to treat adult patients with Amyotrophic Lateral Sclerosis (ALS), a fatal neurodegenerative disease. Participants received an injection of a neurotrophic factor (G-CSF, Granulocyte-Colony Stimulating Factor) to stimulate the neuronal differentiation of adult NSCs in the brain [11].

Since, other clinical trials using endogenous or derived NSCs were conducted in the world to treat several brain disorders.

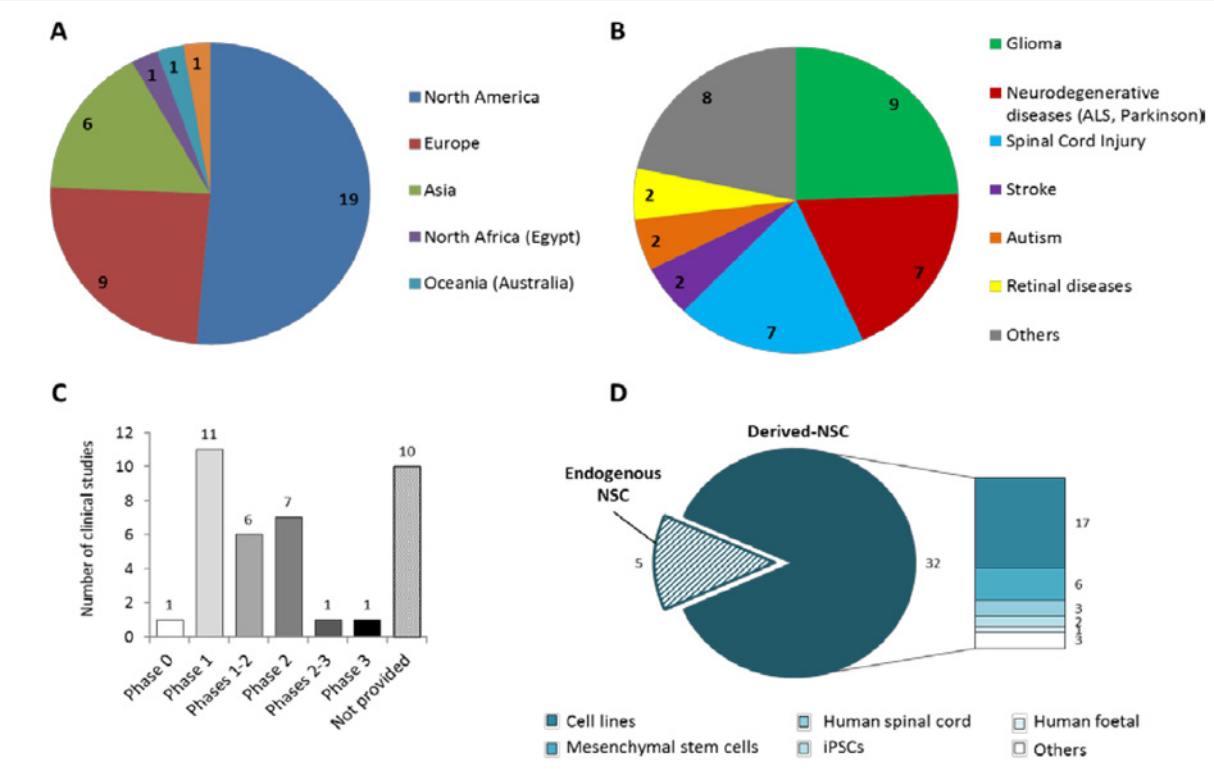

Figure 1 Clinical trials using neural stem cells in the world.
Distribution of clinical trials with neural stem cells by countries (A), according to diseases (B), and according their randomized phases (C). Distribution of clinical trials using endogenous neural stem cells, or derived-neural stem cells (D).
Abbreviations: ALS: Amyotrophic Lateral Sclerosis; iPSCs: induced Pluritotent Stem Cells; NSC: Neural Stem Cell.

Most of them were found in North America (19), few in Europe (United Kingdom (4), Switzerland (2), Italy (2) and Belgium (1)), and in Asia (China (4), India (1), Taiwan (1)).Isolated studies were initiated in Egypt, Australia, and Russian federation (Figure 1A). The use of NSCs in clinical trials were mainly developed against gliomas, neurodegenerative diseases (ALS and Parkinson), and spinal cord injuries. Other studies were conducted for the treatment of strokes, autism and retinal disorders (Figure 1B). Among these clinical studies, only one was in phase 3 and one in phases 2-3 (Figure 1C). Currently, 18 clinical trials are still progressing, for which first results and primary or final completion are expected in the next months or years.

Endogenous NSCs were not mainly involved in these clinical trials, whereas derived-NSCs were usually studied. Most clinical trials used NSCs derived from different cell lines, such as HuCNS-SC®, CTX DP, HB1.F3.CD, hCE1m6, ISC-hpNSC, or AST-OPC1. Several studies also used mesenchymal stem cell-derived NSCs, human spinal cord-derived NSCs, induced pluripotent stem cells (iPSCs), or human foetal-derived NSCs. Only 5 clinical trials involved endogenous NSCs (Figure 1D).

SOME EXAMPLES OF CLINICAL TRIALS WITH NEURAL STEM CELLS

The first study using NSCs on children was in 2006 for infantile neuronal ceroid lipofuscinosis (INCL) (NCT00337636) [12]. This disease can affect the brain and the retina of persons from infancy to adulthood age. In juvenile, it is caused by mutation in the CLN1 gene, which codes for a lysosomal protein. This mutation leads a loss of vision and blindness, epilepsy, motor coordination problems or emotional reactions like depression [13]. Human central nervous system-stem cells (HuCSN-SCs), *in vitro*, had been showed to secrete the enzyme deficient in INCL. In this clinical trial, HuCNS-SCs from single human foetal brain tissue have been transplanted in each lateral ventricle of infants. The procedure seemed both safe and well accepted by children. Only transitory moderate or severe adverse effects were observed, and these were not directly attributed to the transplantation. Importantly, discovery of HuCNS-SCs in post-mortem host brain 1-year after transplantation and long after the cancellation of immunosuppression suggested that this approach has a therapeutic potential for the treatment of human neurodegenerative disease, in children but also in adult. Currently, this investigation measures the post-transplantation disease progression under clinical trial protocol n°NCT01238315.

The ALS is a neurodegenerative disease caused by a progressive degeneration of motor neurons. The death is generally caused by respiratory failure few years after the appearance of first symptoms. The dysphagia and pneumonia are the most important symptoms, which both reach the life quality of patients. There is no cure for this disease except some management to reduce symptoms or the Riluzole® administration which counteracts the excitotoxicity and allows a low survival improvement (3-6 months) [14]. Thirty clinical trials have started

Table 1: Clinical trials that involved neural stem cells (according to the website: www.clinicaltrials.gov).

Identifier	Pathology	Phase	Age group	Study start	Country	Completion
NCT02055196	Recurrent high-grade gliomas	1	Adult	*np*	US	may 2014
NCT01172964	Recurrent high-grade gliomas	*np*	Child/Adult/Senior	2010	US	feb. 2015
NCT01478854	GBM (newly diagnosed)	*np*	Adult/Senior	2011	US	jan. 2016
NCT00581113	Brain metastases	3	Adult/Senior	2007	US	jun. 2009
NCT01251913	Ependymomas/Gliomas/ PNET/ Pineal Tumours/ PCNSL	*np*	Adult/Senior	2010	US	apr. 2015
NCT00397423	Amyotrophic Lateral Sclerosis	2	Adult	2006	CN	aug. 2007
NCT01640067	AmyotrophicLateralSclerosis	1	Adult/Senior	2011	IT	dec. 2015
NCT00976430	Parkinson	*np*	Adult/Senior	2009	IN	nov. 2011
NCT01321333	Thoracic Spinal Cord Injury	1 / 2	Adult	2011	CAN, CHE	apr. 2015
NCT01772810	Spinal Cord Injury	1	Adult	2014	US	mar. 2016
NCT02163876	Cervical Spinal CordInjury	2	Adult	2014	US, CAN	may 2016
NCT01725880	Spinal Cord Injury	*np*	Adult	2012	CHE	may 2016
NCT01343511	Autism	1 / 2	Child	2009	CN	may 2011
NCT01632527	Age-related MD	1 / 2	Adult/Senior	2012	US	jun. 2015
NCT01432847	Retinal Disease	*np*	Child/Adult/Senior	2011	US	*np*
NCT01238315	NCL	1	Child	2010	US	apr. 2011
NCT01489267	Hereditary Cerebellar Ataxia	2	Adult	2011	CN	july 2014
NCT02387749	DPN	2 / 3	Adult	2014	EG	aug. 2016

Abbreviations: CAN: Canada; CHE: Switzerland; CN: China; DPN: Diabetic Peripheral Neuropathy; EG: Egypt; GBM: Glioblastoma Multiform; IN: India; IT: Italy; np: not provided; MD: Macular Degeneration; NCL: Neuronal Ceroid Lipofuscinosis; PCNSL: Primary CNS Lymphoma; PNET: Primitive Neuroectodermal Tumours; US: United States.

Table 2: Clinical trials currently ongoing that involve neural stem cells (according to the websit0e: www.clinicaltrials.gov).

Identifier	Pathology	Phase	Age group	Studystart	Country	Completion
NCT02458508	Glioblastoma	*np*	Adult/Senior	2015	IT	mar. 2017
NCT02015819	Recurrent high-grade gliomas	1	Adult/Senior	2014	US	oct. 2017
NCT02192359	Recurrent high-grade gliomas	1	Adult	2016	US	mar. 2019
NCT02177578	GBM (newlydiagnosed)	2	Adult/Senior	2014	US	jun. 2020
NCT01730716	Amyotrophic Lateral Sclerosis	2	Adult/Senior	2013	US	nov. 2016
NCT01348451	Amyotrophic Lateral Sclerosis	1	Adult/Senior	2009	US	dec. 2016
NCT01329926	Parkinson	0	Adult/Senior	2011	US	oct. 2016
NCT02452723	Parkinson	1	Adult/Senior	2016	AU	mar. 2019
NCT02688049	Spinal Cord Injury	1 / 2	Adult	2016	CN	dec. 2017
NCT02302157	Spinal Cord Injury	1 / 2	Adult/Senior	2015	US	sept. 2018
NCT02326662	Spinal Cord Injury	1 / 2	Adult	2014	RU	dec. 2018
NCT02117635	Stroke	2	Adult/Senior	2014	GB	dec. 2017
NCT01151124	Stroke	1	Adult/Senior	2010	GB	mar. 2023
NCT01933802	Multiple Sclerosis	1	Adult/Senior	2014	US	jun. 2017
NCT02720939	Autism Spectrum Disorder	*np*	Child/Adult/Senior	2016	TWN	dec. 2016
NCT01392989	MDS/MPD	2	Adult Senior	2011	US	jan. 2018
NCT01916369	Peripheral Arterial Disease	1	Adult/Senior	2014	GB	dec. 2016
NCT02696746	Channelopathies	*np*	Adult Senior	2012	GB	jan. 2019
NCT02336802	Anxiety	*np*	Adult	2015	BEL	dec. 2018

Abbreviations: AU: Australia; BEL: Belgium; CN: China; GB: United Kingdom; GBM: Glioblastoma Multiform; IT: Italy; np: not provided; MDS: Myelodysplastic Syndromes; MPD: Myeloproliferative Disorders; RU: Russian Federation; TWN: Taïwan; US: United States

with different stem cells (hematopoietic, mesenchymal, neural or again adipocyte-derived stem cells). Three studies were well documented with NSCs that we will describe here.

The two first clinical trials (NS2008-1 and NCT01348451) used NSCs isolated from the cervico-thoracic spinal cord-derived from an 8-week gestation foetus (NSI-566RSC cell line). They were isolated and propagated *in vitro* in serum-free medium until 25 passages and used to be injected in patients. These human spinal cord-derived stem cells (HSSCs) have been used in clinical trials for 15 patients with ALS [15,16]. In these two trials, HSSCs were injected five times into the lumbar or cervical segments of the spinal cord of ALS patients by unilateral or bilateral injections. 6 patients received first either unilateral or bilateral lumbar injection [15]. In the second part of the trial, 3 patients who had already received bilateral injection in lumbar, received unilateral injection in cervical and 3 other patients received unilateral cervical injection [16].

The goal of these studies was to show the safety and tolerability of injection in lumbar or cervical spinal cords of patients and check the dual-targeting approach.

Firstly, some adverse events were noted like encephalopathy, bronchitis and pneumonia but these side effects were due to the ALS diseases. Most patients had mild and transient pain but the major toxicity was related to immunosuppressant drugs given to all patients. There was no evidence for decline in function or acceleration of progression after surgical intervention. More than 50%of patients had better outcomes than baseline until 15 months post-operation. Despite 7 deaths unrelated to HSSC use, the injection of stem cells in lumbar and cervical spinal cord of patients with ALS represented a significant advance in the cell therapy field. Survived-patients showed a slower progression of the disease and functional improvement. The three subjects who received more injections (bilateral and unilateral injections in lumbar and cervical, respectively) demonstrated the largest effects on progression rates, suggesting the beneficial of multiple injections. Following these clinical trials, phase 2 trial started in September 2013 (Protocol n° NCT01730716).

Another Phase 1 clinical trial started in 2012 (clinical trial number: NCT01640067) with ALS patients and similar transplantation method [17]. However, human NSCs were isolated from forebrain at gestational ages greater than 8th post-conceptional week with spontaneous in utero death. This source of cells could be more ethic because cells were recovered following miscarriage. Moreover, 5 times more cells were transplanted (750000 cells per patient) than the previous clinical trial described above (100 000 cells per patient) [16]. The goal of this study was to approve the safety of both cells and procedure of transplantation. No severe side effect was found except pain near the injection site, and the MRI did not show structural changes or tumour formation in brain or spinal cord after transplantation. This clinical trial reproduced the results from the previously quote clinical trial using other cells. Now, intraspinal injection was evaluated into the cervical spinal cord of 12 ambulatory patients with ALS.

Several investigations showed that NSCs and progenitor cells present in the subventricular zone of brain bearing glioblastoma represent potential tumour-initiating cells (cancer stem cells) associated with a higher recurrence rate and shorter overall survival [18,19]. In the United States, a recent randomized phase 2 clinical trial, with primary completion in June 2020 (NCT02177578), is currently conducted in newly diagnosed glioblastoma patients, in order to treat endogenous NSCs in the subventricular zone with modified radiation treatment in addition to the standard chemotherapy (Temozolomide). A group of patients is treated with a higher radiation therapy plan, both directed against tumour and subventricular zone. And the control group is treated with standard radiation therapy, only directed against the tumour. The aim of this study is to examine the progression free survival between these two groups.

Several other studies concerning brain diseases like cerebellar atrophy [20], spinal cord injury [21], Pelizaeus-Merzbacher disease [22] or cerebral palsy [23] also showed safety of the procedure and efficiency of autologous or allogenic stem cells transplantation after expansion *in vitro*.

DISCUSSION & CONCLUSION

As documented above, derived-neural stem cells are mainly used for brain disorders like cancers, neurodegenerative diseases or diseases from the peripheral nervous system. Collecting endogenous NSCs cells directly from the brain is complicated and the use of derived-NSCs from other stem cells could lead mutation issues. One of the best strategies to reach NSCs without taking them out from their environment would be to target NSCs directly in the brain by intra-ventricular injection. Several experimental procedures were recently developed to target *in vitro* and *in vivo* NSCs and to induce their differentiation. For instance, aneurofilament derived-peptide, named NFL-TBS.40-63, is able to target NSCs from the subventricular zone. Moreover, *in vitro* the peptide decreased the self-renewal and proliferation of NSCs cells while their adhesion and differentiation were increased [24]. Another study showed that the forced neuronal differentiation of glioblastoma stem-like cells with neurogenic transcription factors inhibited their capacity to form orthotopictumour *in vivo* [25]. Glioblastoma stem cells are implicated in the tumour recurrence and thus in the low survival rate of patients. Targeting these cells is a promising approach to treat this disease [26].

As describe above, the first clinical trial using a factor to stimulate endogenous NSCs started in 2006 in China in a cohort with ALS patients. This clinical trial in phase 2 was finished since 2007 (according to the website clinicaltrials.org), but no results are available. Since the first clinical trial involving NSCs in 2006, 36 others clinical trials came out, and only one is in phase 3. Unfortunately, most studies are outdated and only few results are published. The most promising strategy would be to target endogenous NSCs directly in the brain of patients by intraventricular injection to induce the differentiation in the case of neurodegenerative diseases or to stop their migration and tumorigenesis in the case of tumour.

ACKNOWLEDGEMENTS

This work was supported by AFM (Association Françaisecontre les Myopathies, ARC (Association de Recherchecontre le Cancer), CIMATH (CiblageMoléculaireetThérapeutique), MATWIN

(Maturation & Accelerating Translation with Industry), and by UNAM (Université Nantes, Angers, Le Mans).

Barreau Kristell is supported by a grant of the University of Angers, in the framework of NanoFar "European Doctorate in Nanomedicine" EMJD programme funded by EACEA. Lépinoux-Chambaud Claire is supported by the "Société d'Accélération du Transfert de Technologie (SATT) Ouest Valorisation".

REFERENCES

1. Cheuk DK. Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies. World J Transplant. 2013; 3: 99-112.
2. Park Y-J, Cha S, Park Y-S. Regenerative Applications Using Tooth Derived Stem Cells in Other Than Tooth Regeneration: A Literature Review. Stem Cells Int. 2016: 9305986.
3. BaghabanEslaminejad M, Malakooty Poor E. Mesenchymal stem cells as a potent cell source for articular cartilage regeneration. World J Stem Cells. 2014; 6: 344-354.
4. Yamaguchi M, Seki T, Imayoshi I, Tamamaki N, Hayashi Y, Tatebayashi Y, et al. Neural stem cells and neuro/gliogenesis in the central nervous system: understanding the structural and functional plasticity of the developing, mature, and diseased brain. J Physiol Sci. 2016; 66: 197-206.
5. Chang YS, Ahn SY, Yoo HS, Sung SI, Choi SJ, Oh WI, et al. Mesenchymal stem cells for bronchopulmonary dysplasia: phase 1 dose-escalation clinical trial. J Pediatr. 2014; 164: 966-972.
6. Nait-Oumesmar B, Picard-Riera N, Kerninon C, Decker L, Seilhean D, Höglinger GU, et al. Activation of the subventricular zone in multiple sclerosis: evidence for early glial progenitors. Proc Natl Acad Sci U S A. 2007; 104: 4694-4699.
7. Müller F-J, Snyder EY, Loring JF. Gene therapy: can neural stem cells deliver? Nat Rev Neurosci. 2006; 7: 75-84.
8. Zong H, Parada LF, Baker SJ. Cell of Origin for Malignant Gliomas and Its Implication in Therapeutic Development. Cold Spring Harb Perspect Biol. 2015; 7: 020610.
9. Kim SU, Lee HJ, Kim YB. Neural stem cell-based treatment for neurodegenerative diseases. Neuropathol. 2013; 33: 491-504.
10. Bexell D, Svensson A, Bengzon J. Stem cell-based therapy for malignant glioma. Cancer Treat Rev. 2013; 39: 358-365.
11. Fan D, Zhang J, Deng M, Kang D, Zheng J, Xu Y, et al. Basic and clinical researches on amyotrophic lateral sclerosis/motor neuron disease. Beijing Da Xue Xue Bao. 2009; 41: 279-281.
12. Selden NR, Al-Uzri A, Huhn SL, Koch TK, Sikora DM, Nguyen-Driver MD, et al. Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis. J Neurosurg Pediatr. 2013; 11: 643-652.
13. von Tetzchner S, Fosse P, Elmerskog B. Juvenile neuronal ceroid lipofuscinosis and education. Biochim Biophys Acta. 2013; 1832: 1894-1905.
14. Orsini M, Oliveira AB, Nascimento OJM, Reis CHM, Leite MAA, de Souza JA, et al. Amyotrophic Lateral Sclerosis: New Perpectives and Update. Neurol Int. 2015; 7: 5885.
15. Glass JD, Boulis NM, Johe K, Rutkove SB, Federici T, Polak M, et al. Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients. Stem Cells. 2012; 30: 1144-1151.
16. Feldman EL, Boulis NM, Hur J, Johe K, Rutkove SB, Federici T, et al. Intraspinal neural stem cell transplantation in amyotrophic lateral sclerosis: phase 1 trial outcomes. Ann Neurol. 2014; 75: 363-373.
17. Mazzini L, Gelati M, Profico DC, Sgaravizzi G, ProjettiPensi M, Muzi G, et al. Human neural stem cell transplantation in ALS: initial results from a phase I trial. J Transl Med. 2015; 13: 17.
18. Chen L, Guerrero-Cazares H, Ye X, Ford E, McNutt T, Kleinberg L, et al. Increased Subventricular Zone Radiation Dose Correlates with Survival in Glioblastoma Patients After Gross Total Resection. Int J Radiat Oncol Biol Phys. 2013; 86: 616-622.
19. Jafri NF, Clarke JL, Weinberg V, Barani IJ, Cha S. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neuro Oncol. 2013; 15: 91-96.
20. Tian Z, Chen T, Zhong N, Li Z, Yin F, Liu S. Clinical study of transplantation of neural stem cells in therapy of inherited cerebellar atrophy. Beijing Da Xue Xue Bao. 2009; 41: 456-458.
21. Moviglia GA, Fernandez Viña R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G, et al. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. Cytotherapy. 2006; 8: 202-209.
22. Gupta N, Henry RG, Strober J, Kang S-M, Lim DA, Bucci M, et al. Neural stem cell engraftment and myelination in the human brain. Sci Transl Med. 2012; 4: 137.
23. Chen G, Wang Y, Xu Z, Fang F, Xu R, Wang Y, et al. Neural stem cell-like cells derived from autologous bone mesenchymal stem cells for the treatment of patients with cerebral palsy. J Transl Med. 2013; 11: 21.
24. Lépinoux-Chambaud C, Barreau K, Eyer J. The Neurofilament-Derived Peptide NFL-TBS.40-63 Targets Neural Stem Cells and Affects Their Properties. Stem Cells Transl Med. 2016; 5: 901-913.
25. Guichet P-O, Bieche I, Teigell M, Serguera C, Rothhut B, Rigau V, et al. Cell death and neuronal differentiation of glioblastoma stem-like cells induced by neurogenic transcription factors. Glia. 2013; 61: 225-239.
26. Pointer KB, Clark PA, Zorniak M, Alrfaei BM, Kuo JS. Glioblastoma cancer stem cells: Biomarker and therapeutic advances. Neurochem Int. 2014; 71: 1-7.

Cite this article

Barreau K, Lépinoux-Chambaud C, Eyer J (2016) Review of Clinical Trials Using Neural Stem Cells. JSM Biotechnol Bioeng 3(3): 1057.