NEURAL REGENERATION RESEARCH
September 2014, Volume 9, Issue 17
www.nrronline.org

Stem cell transplantation for treating stroke: status, trends and development

Wenxin Huo, Xiaoyang Liu, Cheng Tan, Yingying Han, Chunyang Kang, Wei Quan, Jiajun Chen

Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun, Jilin Province, China

Corresponding author:
Jiajun Chen, M.D., Department of Neurology, China-Japan Union Hospital of Jilin University, Changchun 130033, Jilin Province, China, chenjiajun999@sina.com.

doi:*10.4103/1673-5374.141793*
http:*//www.nrronline.org/*

Accepted: *2014-08-10*

Abstract

The developing approaches of thrombolytic therapy, endovascular treatment, neuroprotective therapy, and stem cell therapy have enabled breakthroughs in stroke treatment. In this study, we summarize and analyze trends and progress in stem cell transplantation for stroke treatment by retrieval of literature from Thomson Reuters Web of Science database, the NIH Clinical Trial Planning Grant Program, and Clinical Trials Registration Center in North America. In the last 10 years, there has been an increasing number of published articles on stem cell transplantation for stroke treatment. In particular, research from the USA and China has focused on stem cell transplantation. A total of 2,167 articles addressing stem cell transplantation for stroke treatment from 2004 to 2013 were retrieved from the Thomson Reuters Web of Science database. The majority of these articles were from the USA (854, 39.4%), with the journal *Stroke* publishing the most articles (145, 6.7%). Of the published articles, 143 were funded by the National Institutes of Health (accounting for 6.6% of total publications), and 91 by the National Natural Science Foundation of China. Between 2013 and 2014, the National Institutes of Health provided financial support ($130 million subsidy) for 329 research projects on stroke therapy using stem cell transplantation. In 2014, 215 new projects were approved, receiving grants of up to $70,440,000. Ninety clinical trials focusing on stem cell transplantation for stroke were registered in the Clinical Trial Registration Center in North America, with 40 trials registered in the USA (ranked first place). China had the maximum number of registered research or clinical trials (10 projects).

Key Words: *nerve regeneration; stem cell; stroke; transplantation; neural stem cell; bone marrow mesenchymal stem cell; umbilical cord blood stem cell; embryonic stem cell; neural regeneration*

Huo WX, Liu XY, Tan C, Han YY, Kang CY, Quan W, Chen JJ. Stem cell transplantation for treating stroke: status, trends and development. Neural Regen Res. 2014;9(17):1643-1648.

Introduction

Stroke is the collective name for cerebrovascular disease with brain functional deficits due to a number of causes. Stroke is associated with high morbidity, mortality, and disability rates, and is regarded as one of three major lethal diseases in most countries because of increasing morbidity and mortality (Bliss et al., 2007; Li et al., 2009). Stem cell transplantation offers a new avenue for stroke treatment, and has been used to treat stroke for the last 10 years (Kalluri et al., 2008). Stem cells are used to replace necrotic nerve tissue, and thereby contribute to neural network reconstruction through a number of mechanisms, including replacing necrotic neurons with new functional neurons, maintaining neural circuits and reconstructing neural conduction pathways by replacing necrotic glial cells, providing nutrients for tissue at the peri-infarct penumbra, and promoting survival, transfer, and differentiation of endogenous progenitors through neurotrophic factor secretion. After transplantation, both endogenous and exogenous neural stem cells migrate to the distal injury area and differentiate into new nerve cells, promoting tissue restoration and functional restoration in the central nervous system, particularly after cerebral infarction (Thored et al., 2006; Zheng et al., 2009). A variety of stem cells have been used in stroke treatment, including neural, bone marrow mesenchymal, umbilical cord blood, and embryonic stem cells (Darsalia et al., 2005; Liu, 2013). Although these stem cells are derived from different cell types, they share a similar theoretical basis in treatment of ischemic stroke, namely cell replacement, immunomodulation, neuroprotection, and neurotrophy, which contribute to relieving nerve damage and promoting functional recovery (Hasegawa et al., 2006; Sensebé et al., 2010). The mode of transplantation is one component of efficient stem cell transplantation for stroke treatment, and commonly used approaches involve direct, intravenous, or arterial injections. Moreover, the choice of stem cells (neural, bone marrow mesenchymal, umbilical cord blood or embryonic) is also key to stem cell transplantation (Darsalia et al., 2007). Efficacy of stroke treatment using stem cells is determined by the stem cell source, transplantation approach, stem cell survival and host integration, and treatment safety (Arvidsson et al., 2002; Ourednik et al., 2002), although many questions are unanswered: how can stem cell transplantation success in clinical practice be achieved in a safe and rapid manner based on current clinical trial results? And what are the mechanisms of action? Further efforts are needed to explore treatment profiles (Zhao et al., 2002; Kawai et al., 2010). In this study, we analyzed published literature on stroke stem cell transplantation by examining funded and registered studies.

Trends from Published Articles about Stem Cell Transplantation for Stroke Treatment

Computer-based retrieval was performed using Thomson Reuters Web of Science database (http://webofknowledge.com/), the National Institutes of Health (NIH) Common Fund database (http://www.nih.gov/), and Clinical Trial Registration Center in North America (http://www.clinicaltrials.gov/), between 2004-01-01 and 2013-12-31. Key words used were "stem cell", "stroke", "transplantation", "neural stem cells", "mesenchymal stem cells", "bone marrow mesenchymal stem cells", "bone mesenchymal stem cells", "adipose-derived stem cells", "umbilical cord blood stem cells", and "embryonic stem cell".

Inclusion criteria

Any article about stem cell transplantation for stroke treatment was included.

Exclusion criteria

(1) Articles without the authors' approval; and (2) unpublished articles.

Literature analysis

Included articles were quantitatively and qualitatively analyzed using the following categories: publication time, publication nation and region, article type, institution distribution, and publication sources. Analysis methods included retrieval from Web of Science and NIH Common Fund databases, analysis functions in the Clinical Trial Registration Center in North America, and graphics functions of Excel software. Article types included original research, reviews, conference abstracts, conference articles, editorials, and chapters.

Results

Efficacy of stem cell transplantation for stroke treatment

We initially compared the advantages and disadvantages of using different stem cell types for transplantation in stroke treatment (**Table 1**).

Literature analysis of the Web of Science database between 2004 and 2013

Number of articles on different stem cell types for stroke treatment

Next, we determined the number of articles published in the Web of Science database between 2004 and 2013, on different types of stem cell transplantation for stroke treatment (**Table 2**).

Of the included articles, those focusing on neural stem cell transplantation have sharply increased, followed by bone marrow stem cell transplantation. Articles about embryonic and umbilical cord blood stem cell transplantation do not show significant increases. In total, 2,617 related articles were assessed, including 87 articles published in 2004, 102 in 2005, 146 in 2006, 159 in 2007, 170 in 2008, 262 in 2009, 280 in 2010, 319 in 2011, 312 in 2012, and 388 in 2013. Therefore, the number of stroke treatment related articles published in the Web of Science database has increased within the last 5 years, with the maximum published in 2013.

Highly cited articles on stem cell transplantation for stroke treatment

According to bibliometrics, citation frequency is the main indicator for determining literature quality and reflects the academic value of peer reviews, with higher citation frequencies indicating greater scientific value (Zhou et al., 2005; Yue et al., 2008). Thus, we determined highly cited articles from the 2,617 related articles identified from the Web of Science database between 2004 and 2013 (**Table 3**).

Analysis of publication countries

Publication countries of included articles identified from the Web of Science database between 2004 and 2013 were analyzed (**Figure 1**).

Of the 2,167 published articles, the USA has published the most (854 articles, 39.4%), followed by China (361 articles), Japan (198 articles), Germany (173 articles), South Korea (157 articles), UK (120 articles), Canada (112 articles), and other countries (< 100 articles) (Figure 2). There are three Asian countries in the top nine, showing regional dominance in this research field.

Analysis of article type

The majority of articles published were original research (up to 1,535 articles, 70.8%), followed by reviews (395 articles, 18.3%), meeting abstracts (147 articles), and other types (< 100 articles) (**Table 4**).

Analysis of publication institutions

Publication institutions of included articles were analyzed (**Figure 2**).

Of the top ten institutions publishing articles on stem cell transplantation for stroke treatment, Oakland University occupies first place (83 articles, 3.8%), followed by the Henry Ford Hospital (77 articles), University of Florida (68 articles), and Stanford University (63 articles). The majority of publication institutions are located in the USA, although Fudan University and Asia University are also ranked in the top ten.

Analysis of publication journals

The majority of included articles were published in brain science journals, including *Stroke* (145 articles, 6.7%), *Brain Research* (72 articles), *Cell Transplantation* (70 articles), *Journal of Cerebral Blood Flow and Metabolism* (63 articles), *PLOS ONE* (57 articles), *Experimental Neurology* (51 articles), and other journals (< 50 articles) (**Table 5**). Statistical analysis of publication journals enables researchers and physicians to identify key journals and determine relevant literature on stem cell transplantation for stroke treatment. In turn this will guide submission and improve acceptance rates, which is conducive to expanding research achievements.

Analysis of funding agencies

The funding agencies responsible for published articles were determined (**Table 6**).

Table 1 Different stem cell types for stroke treatment

Cell types	Advantages	Disadvantages
Neural stem cells	Neural stem cells can proliferate, differentiate, and migrate into the ischemic area, have strong capacity of restoration and high survival rate.	Neural stem cells have limited self-renewal and pluripotency capabilities *in vitro*.
Bone marrow mesenchymal stem cells	Bone marrow mesenchymal stem cells have pluripotent differentiation potential and easy access for harvesting and amplification; these cells are involved in endogenous neurogenesis.	The optimal transplantation approach and the number of transplanted cells need further exploration, as well as the assessment of transplantation efficacy and safety.
Embryonic stem cells	Embryonic stem cells can be massively amplified and have pluripotent potentials, these cells can differentiate into all types of cells *in vivo*.	The application of embryonic stem cells is restricted by incomplete culture methods, transplantation rejection and risk of tumor formation, ethics problem.
Umbilical cord blood stem cells	Umbilical cord blood stem cells have easy and wide sources, low immune rejection, and application potential in clinics	Due to low immunogenicity, low antigen expression and low activities, umbilical cord blood stem cells cannot be massively separated, purified, amplified and stored.

Table 2 Number of articles published on different types of stem cell transplantation for stroke treatment

Publication time (year)	Type of cells/literatures (*n*)			
	Neural stem cells	Bone marrow mesenchymal stem cells	Embryonic stem cells	Umbilical cord blood stem cells
2004	53	6	11	6
2005	47	16	17	7
2006	72	21	23	12
2007	94	20	25	10
2008	96	41	29	14
2009	141	60	44	19
2010	124	78	32	26
2011	141	62	25	26
2012	141	91	28	25
2013	183	122	31	24

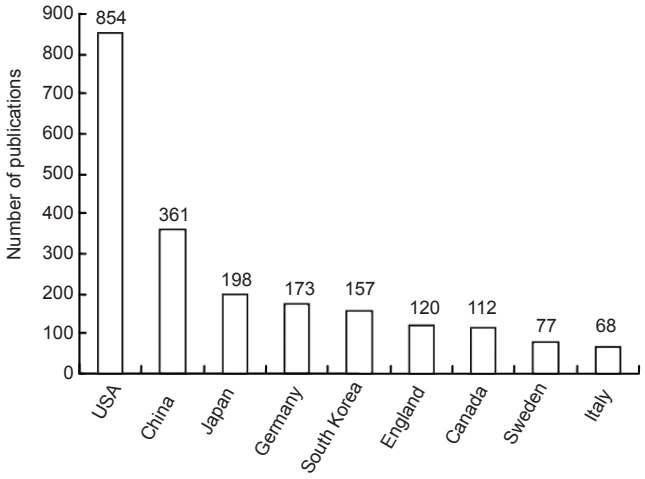

Figure 1 Top 9 countries publishing articles on stem cell transplantation for stroke treatment.

Table 3 Highly cited articles on stem cell transplantation for stroke treatment

Title	First author	Journal	Publication time (year)	Total citation frequency	Average citation frequency
Transplanted human fetal neural stem cells survive, migrate, and differentiate in ischemic rat cerebral cortex	Kelly S	*Proceedings of the National Academy of Sciences of the USA*	2004	293	26.64
The science of stroke: mechanisms in search of treatments	Moskowitz MA	*Neuron*	2010	287	57.40
Central nervous system entry of peripherally injected umbilical cord blood cells is not required for neuroprotection in stroke	Borlongan CV	*Stroke*	2004	230	20.91
Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats	Zhang RL	*Journal of Cerebral Blood Flow and Metabolism*	2004	212	19.27
Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells	Shyu WC	*Circulation*	2004	203	18.45
SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: Association with bone marrow cell homing to injury	Hill WD	*Journal of Neuropathology and Experimental Neurology*	2004	194	17.64
Mesenchymal stem cells that produce neurotrophic factors reduce ischemic damage in the rat middle cerebral artery occlusion model	Kurozumi K	*Molecular Therapy*	2005	193	19.30

Table 4 Types of published articles on stem cell transplantation for stroke treatment

Type	Number of publications	Percentage (%)
Article	1,535	70.8
Review	395	18.2
Meeting abstract	147	6.8
Proceedings paper	79	3.7
Editorial material	46	2.1
News item	13	0.6

Meeting abstracts may also be included as original research, therefore the total number of all types of articles is higher than the number of included articles.

Table 5 Top ten journals publishing articles on stem cell transplantation for stroke treatment

Journal	Number of publications	Percentage (%)
Stroke	145	6.7
Brain Research	72	3.3
Cell Transplantation	70	3.2
Journal of Cerebral Blood Flow and Metabolism	63	2.9
PLOS ONE	57	2.6
Experimental Neurology	51	2.4
Journal of Neuroscience Research	41	1.9
Neuroscience	34	1.6
Neuroscience Letters	33	1.5
Neural Regeneration Research	28	1.3

Table 6 Funding agencies responsible for published articles on stem cell transplantation for stroke treatment

Funding agency	Number of publications	Percentage (%)
National Institutes of Health	143	6.6
National Natural Science Foundation of China	91	4.2
European Union	39	1.8
Swedish Research Council	24	1.1
NIH NINDS	23	1.1

The majority of published articles were financially supported by NIH (143 articles, 6.6%), the National Natural Science Foundation of China (91 articles, 4.2%), and other agencies (< 50 articles).

NIH-funded ongoing projects on stem cell transplantation for stroke treatment

NIH not only conducts scientific research engaged in medical fields, but also provides major biomedical research funding to non-NIH research facilities, such as universities, medical colleges, hospitals, and other research institutions. In addition, NIH assists in staff training and promotes exchange of medical information.

During 2013–2014, NIH provided financial support for 329 ongoing research projects on stem cell transplantation in stroke treatment (**Table 7**), with total funding of over $130 million. In 2014, 215 projects were newly approved, with funding of $70,440,000 and an average project fund of $328,000. Of the 329 NIH-funded research projects, 141 articles were financially supported by the National Institute of Neurological Disorders and Stroke, with up to $58,700,000 of subsidy and an average project fund of $416,000. The NIH Heart, Lung, and Blood Institute was second, with total funds of up to $15,020,000.

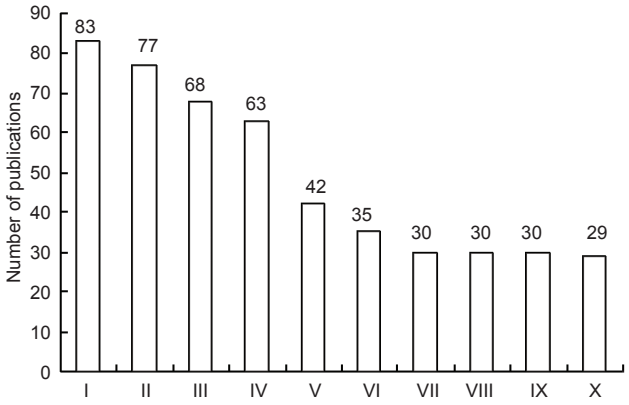

Figure 2 Top ten institutions publishing articles on stem cell transplantation for stroke treatment.
I: Oakland University; II: Henry Ford Hospital; III: University of Florida; IV: Stanford University; V: The University of British Columbia; VI: Harvard University; VII: Yale University; VIII: Fudan University; IX: Ajou University; X: Medical College of Georgia.

Table 7 Number of ongoing NIH projects and funding for stem cell transplantation in stroke treatment

Fiscal year	Projects	Project funding	% of total funding
2010	2	$3,480,000	2.6
2011	5	$2,745,327	2.1
2012	19	$9,992,988	7.6
2013	88	$45,614,937	34.5
2014	215	$70,444,022	53.3
Total	329	132,277,274	100

Table 8 Regions of registered clinical trials on stem cell transplantation for stroke treatment in the North American Clinical Trial Data Center

Region	Number of Studies
North America	43
Europe	25
East Asia	11
Middle East	1
South America	2
South Asia	5
Southeast Asia	3
World	90

Analysis of the Clinical Trial Registration Program in North America

The North American Clinical Trial Data Center (http://www.

clinicaltrials.gov/) was jointly developed by the NIH, National Library of Medicine (NLM), and United States Food and Drug Administration (FDA) in February 2000. The aim of the North American Clinical Trial Data Center is to report in a timely manner, clinical trial information sponsored by NIH, other National Government Agencies, and the American Medical Association, and provide related services for patients and their families, medical staff and the public. As stipulated by NIH, any clinical trial targeting experimental treatments for serious or life-threatening diseases and conditions are registered, regardless of funding is provided nationally or privately. Registration aims to share progress of all world-wide clinical trials through the internet.

The North American Clinical Trial Data Center includes nearly 180,000 clinical trials funded by NIH, other federal government agencies, and private enterprises, and receives > 50 million page views per month and > 65,000 visitors per day. Of all registered clinical trials, 52,381 projects were from the USA (accounting for 51%), while over 7,000 clinical trials were registered by Chinese researchers. Registration areas for clinical trials on stem cell transplantation for stroke treatment are shown (**Table 8**).

Ninety clinical trials are registered in the North American Clinical Trial Data Center. Of these, 40 projects are registered in North America (ranked first place), followed by Europe, with the UK responsible for seven projects, France six, Germany six, and Spain four. In Asia, China has the most ongoing research projects or completed clinical trials ($n = 10$).

Discussion

In the past 10 years, an increasing amount of literature has highlighted the use of stem cell transplantation for stroke treatment. In 2008, only 87 articles were published, increasing to 388 in 2013. Different stem cell types have been widely applied for stroke treatment, with a sharp increase in the number of studies addressing neural stem cell transplantation, followed by bone marrow mesenchymal stem cell transplantation. Embryonic and umbilical cord blood stem cell transplantation are rarely documented, showing no significant increase in number of related studies.

We found that from 2004–2013, the USA is the most SCI-indexed country for articles on stem cell transplantation for stroke treatment, publishing the most literature and highlighting the contribution of this country to medical research in the stroke field. China ranks second, publishing 292 articles. The top publication institutions for articles are Oakland University, Henry Ford Hospital, and University of Florida, all located in the USA. Knowledge of key institutions for stem cell transplantation will facilitate technical exchange and research cooperation among experts.

Of the funding agencies responsible for supporting projects on stem cell transplantation for stroke treatment, NIH provides financial support for 143 articles (accounting for 6.6% of total literature), while the National Natural Science Foundation of China funded 91 articles, demonstrating China's contribution to the field of stem cell transplantation.

At present, NIH provides considerable funds for medical research addressing stem cell transplantation for stroke treatment, funding 329 ongoing projects with over $130 million of total subsidy.

Among the 90 clinical trials registered in the North America Clinical Trial Data Center, 40 projects were registered in North America (occupying first place), followed by Europe with UK (7 projects), France (6 projects), Germany (6 projects), and Spain (4 projects). In Asia, China has the maximum ongoing research or completed clinical trials (10 projects).

In recent years, stem cell transplantation has become a hot spot for stroke treatment, but its clinical application has been greatly restricted (Buchan et al., 2001; Pollock et al., 2006). Further work is needed to determine a stem cell source, transplantation approach, safety of cell transplantation, therapeutic time window, therapeutic dose, route of administration, choice of cell lines, indications, long-term effects and risk assessment, stem cell survival and integration in the host (Nelson et al., 2002; Chu et al., 2004). Currently, there is no strong evidence showing that transplanted stem cells can replace damaged cells, reconstruct neural circuits, or improve loss of function after stroke (Fan et al., 2010; Darsalia et al., 2011), and many questions remain. For example, how can neurological recovery in transplant recipients be promoted, and how can tumorigenicity, pathogenicity, and immune rejection of transplanted stem cells be detected? (Bühnemann et al., 2006; Hacke et al., 2008). Resolution of these problems will allow broader application of neural stem cell transplantation.

References

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med 9:963-970.

Bliss T, Guzman R, Daadi M, Steinberg GK (2007) Cell transplantation therapy for stroke. Stroke 38:817-826.

Borlongan CV, Hadman M, Sanberg CD, Sanberg PR (2004) Central nervous system entry of peripherally injected umbilical cord blood cells is not required for neuroprotection in stroke. Stroke 10:2385-2389.

Buchan AM, Warren D, Burnstein R (2001) Transplantation of cultured human neuronal cells for patients with stroke. Neurology 6:821-822.

Bühnemann C, Scholz A, Bernreuther C, Malik CY, Braun H, Schachner M, Reymann KG, Dihné M (2006) Neuronal differentiation of transplanted embryonic stem cell-derived precursors in stroke lesions of adult rats. Brain 12:3238-3248.

Chu K, Kim M, Park KI, Jeong SW, Park HK, Jung KH, Lee ST, Kang L, Lee K, Park DK, Kim SU, Roh JK (2004) Human neural stem cells improve sensorimotor deficits in the adult rat brain with experimental focal ischemia. Brain Res 2:145-153.

Darsalia V, Heldmann U, Lindvall O, Kokaia Z (2005) Stroke-induced neurogenesis in aged brain. Stroke 8:1790-1795.

Darsalia V, Kallur T, Kokaia Z (2007) Survival, migration and neuronal differentiation of human fetal striatal and cortical neural stem cells grafted in stroke-damaged rat striatum. Eur J Neurosci 3:605-614.

Darsalia V, Allison SJ, Cusulin C, Monni E, Kuzdas D, Kallur T, Lindvall O, Kokaia Z (2011) Cell number and timing of transplantation determine survival of human neural stem cell grafts in stroke-damaged rat brain. J Cereb Blood Flow Metab 1:235-242.

Fan Y, Shen F, Frenzel T, Zhu W, Ye J, Liu J, Chen Y, Su H, Young WL, Yang GY (2010) Endothelial progenitor cell transplantation improves long-term stroke outcome in mice. Ann Neurol 4:488-497.

Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 13:1317-1329.

Hasegawa N, Kawaguchi H, Hirachi A, Takeda K, Mizuno N, Nishimura M, Koike C, Tsuji K, Iba H, Kato Y, Kurihara H (2006) Behavior of transplanted bone marrow-derived mesenchymal stem cells in periodontal defects. J Periodontol 6:1003-1007.

Hill WD, Hess DC, Martin-Studdard A, Carothers JJ, Zheng J, Hale D, Maeda M, Fagan SC, Carroll JE, Conway SJ (2004) SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: association with bone marrow cell homing to injury. J Neuropathol Exp Neurol 1:84-96.

Kalluri HS, Dempsey RJ (2008) Growth factors, stem cells, and stroke. Neurosurg Focus 3-4:E14.

Kawai H, Yamashita T, Ohta Y, Deguchi K, Nagotani S, Zhang X, Ikeda Y, Matsuura T, Abe K (2010) Tridermal tumorigenesis of induced pluripotent stem cells transplanted in ischemic brain. J Cereb Blood Flow Metab 8:1487-1493.

Kelly S, Bliss TM, Shah AK, Sun GH, Ma M, Foo WC, Masel J, Yenari MA, Weissman IL, Uchida N, Palmer T, Steinberg GK (2004) Transplanted human fetal neural stem cells survive, migrate, and differentiate in ischemic rat cerebral cortex. Proc Natl Acad Sci U S A 32:11839-11844.

Kurozumi K, Nakamura K, Tamiya T, Kawano Y, Ishii K, Kobune M, Hirai S, Uchida H, Sasaki K, Ito Y, Kato K, Honmou O, Houkin K, Date I, Hamada H (2005) Mesenchymal stem cells that produce neurotrophic factors reduce ischemic damage in the rat middle cerebral artery occlusion model. Mol Ther 1:96-104.

Li HL, Li ZY (2009) Stem cell transplantation for treating ischemic stroke. Zhongguo Zuzhi Gongcheng Yanjiu yu Linchuang Kangfu 19:3755-3758.

Liu J (2013) Induced pluripotent stem cell-derived neural stem cells: new hope for stroke? Stem Cell Res Ther 5:115.

Moskowitz MA, Lo EH, Iadecola C (2010) The science of stroke: mechanisms in search of treatments. Neuron 2:181-198.

Nelson PT, Kondziolka D, Wechsler L, Goldstein S, Gebel J, DeCesare S, Elder EM, Zhang PJ, Jacobs A, McGrogan M, Lee VM, Trojanowski JQ (2002) Clonal human (hNT) neuron grafts for stroke therapy: neuropathology in a patient 27 months after implantation. Am J Pathol 4:1201-1206.

Ourednik J, Ourednik V, Lynch WP, Schachner M, Snyder EY (2002) Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. Nat Biotechnol 11:1103-1110.

Pollock K, Stroemer P, Patel S, Stevanato L, Hope A, Miljan E, Dong Z, Hodges H, Price J, Sinden JD (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke. Exp Neurol 1:143-155.

Sensebé L, Krampera M, Schrezenmeier H, Bourin P, Giordano R (2010) Mesenchymal stem cells for clinical application. Vox Sang 2:93-107.

Shyu WC, Lin SZ, Yang HI, Tzeng YS, Pang CY, Yen PS, Li H (2004) Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells. Circulation 13:1847-1854.

Thored P, Arvidsson A, Cacci E, Ahlenius H, Kallur T, Darsalia V, Ekdahl CT, Kokaia Z, Lindvall O (2006) Persistent production of neurons from adult brain stem cells during recovery after stroke. Stem Cells 3:739-747.

Yue HJ, Liu SF, Liang L (2008) A bibliometric analysis on the technology innovation research in China. Keyan Guanli 5:43-52.

Zhang R, Zhang Z, Wang L, Wang Y, Gousev A, Zhang L, Ho KL, Morshead C, Chopp M (2004) Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. J Cereb Blood Flow Metab 4:441-448.

Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC (2002) Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 1:11-20.

Zheng GZ, Michael C (2009) Neuro restorative therapies for stroke: underlying mechanisms andtranslation to the clinic. Lancet Neural 8:491-500.

Zhou JY, Sun T (2005) A quantitative analysis of digital library research article based on the Web of Science. Qing Bao Ke Xue 10:1521-1525.

Copyedited by Jackson C, James R, Norman C, Yang LJ, Yang Y, Li CH, Song LP, Zhao M