

Cite this article as: Neural Regen Res. 2012;7(16):1272-1279.

Stem cell transplantation for treating Parkinson's disease

Literature analysis based on the Web of Science[★]

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Abstract

OBJECTIVE: To identify global research trends of stem cell transplantation for treating Parkinson's disease using a bibliometric analysis of the Web of Science.

DATA RETRIEVAL: We performed a bibliometric analysis of data retrievals for stem cell transplantation for treating Parkinson's disease from 2002 to 2011 using the Web of Science.

SELECTION CRITERIA: Inclusion criteria: (a) peer-reviewed articles on stem cell transplantation for treating Parkinson's disease which were published and indexed in the Web of Science; (b) type of articles: original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material and news items; (c) year of publication: 2002–2011. Exclusion criteria: (a) articles that required manual searching or telephone access; (b) we excluded documents that were not published in the public domain; (c) we excluded a number of corrected papers from the total number of articles.

MAIN OUTCOME MEASURES: (1) Type of literature; (2) annual publication output; (3) distribution according to journals; (4) distribution according to subject areas; (5) distribution according to country; (6) distribution according to institution; (7) comparison of countries that published the most papers on stem cell transplantation from different cell sources for treating Parkinson's disease; (8) comparison of institutions that published the most papers on stem cell transplantation from different cell sources for treating Parkinson's disease in the Web of Science from 2002 to 2011; (9) comparison of studies on stem cell transplantation from different cell sources for treating Parkinson's disease

RESULTS: In total, 1 062 studies on stem cell transplantation for treating Parkinson's disease appeared in the Web of Science from 2002 to 2011, almost one third of which were from American authors and institutes. The number of studies on stem cell transplantation for treating Parkinson's disease had gradually increased over the past 10 years. Papers on stem cell transplantation for treating Parkinson's disease appeared in journals such as *Stem Cells* and *Experimental Neurology*. Although the United States published more articles addressing neural stem cell and embryonic stem cell transplantation for treating Parkinson's disease, China ranked first for articles published on bone marrow mesenchymal stem cell transplantation for treating Parkinson's disease.

CONCLUSION: From our analysis of the literature and research trends, we found that stem cell transplantation for treating Parkinson's disease may offer further benefits in regenerative medicine.

Key Words

Parkinson's disease; neural stem cells; embryonic stem cells; bone marrow mesenchymal stem cells; cell transplantation; bibliometric analysis; Web of Science; neural regeneration

Abbreviations

PD, Parkinson's disease

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Received: 2012-02-06
Accepted: 2012-04-23
(N20120608005/ZLJ)

Li RH. Stem cell transplantation for treating Parkinson's disease: literature analysis based on the Web of Science. Neural Regen Res. 2012;7(16): 1272-1279.

www.crter.cn
www.nrronline.org

doi:10.3969/j.issn.1673-5374.2012.16.010

INTRODUCTION

Parkinson's disease (PD) is a slow-onset neurodegenerative disorder, with selective loss of substantia nigral dopaminergic neurons and significant reduction of striatal dopamine content. The incidence rate of PD rises with age to about 1% in the population of 65 years of age or older^[1]. PD is caused by a decrease in the level of dopamine in the striatum due to degeneration of dopaminergic neurons. At present, drug treatments and surgery cannot fundamentally solve the problem. With the development of cell replacement therapy, medical professionals are exploring treatment by restoration of dopamine neurotransmitters in the neural circuitry of patients with PD by getting dopaminergic neurons and cell transplantation. In 1988, Lindvall *et al*^[2] first used human embryonic midbrain transplantation for the treatment of idiopathic PD. Later, Freed *et al*^[3] transplanted human embryonic midbrain dopaminergic cells into the brains of Parkinson's patients, which substantially alleviated the clinical symptoms. The pathogenesis of PD is clear, the anatomical localization of the nucleus related to pathogenesis is explicit, animal models have been established, and the results of some clinical trials are favorable. Therefore, PD is regarded as one of the most treatable diseases by stem cell transplantation^[4]. Transplanted stem cells can infiltrate and integrate with diseased tissue, differentiate into dopaminergic neurons to replace damaged cells and reconstruct neuronal circuits to restore nerve function. Commonly used stem cells to treat PD are neural stem cells, embryonic stem cells and bone marrow mesenchymal stem cells. Reynolds and Weiss^[5] proposed the concept of neural stem cells. However, the generally accepted concept was proposed by McKay in 1997^[6]. The concept is that neural stem cells have the ability to differentiate into neurons, astrocytes and oligodendrocytes, they can self-renew and generate a large number of neural cell types. Results of induced differentiation *in vitro* show that different conditions can induce neural stem cells to differentiate into different types of neurons, astrocytes and oligodendrocytes. In addition, differentiated neurons have different phenotypes to perform different functions with neurotransmitters. Therefore, neural stem cell transplantation can have an effect on the pathological process of PD. There was a landmark study of embryonic stem cells to treat PD in 2005. Takagi *et al*^[7] carried out directed induced differentiation of rhesus monkey embryonic stem cells, prepared donor cells that were very similar to endogenous dopaminergic neurons, and transplanted them into a monkey model of PD induced by 1-methyl-4-phenyl-tetrahydropyridine. After

transplantation, positron emission tomography showed that living transplanted cells were able to exert the function of dopaminergic neurons, and significantly improved behavioral symptoms of the monkey model of PD. The 1-methyl-4-phenyl-tetrahydropyridine-induced PD model is very similar to PD in humans, and the experimental results predict the efficacy of clinical application of cell transplantation accurately^[8]. Experimental results *in vitro* show that after induced differentiation by a specific inducer, adult mouse and human mesenchymal stem cells gradually show the morphological characteristics of neurons and express specific markers of neurons such as neuron-specific enolase^[9]. This observation confirms that mesenchymal stem cells can be induced to differentiate into nerve cells *in vitro* by nerve growth factor and brain-derived nerve growth factor^[10]. Our study is designed to compare different cell sources for stem cell transplantation for treating PD from published research papers found on the Web of Science from 2002 to 2011.

DATA SOURCES AND METHODOLOGY

Data retrieval

In this study, we used bibliometric methods to quantitatively and qualitatively investigate research trends in studies of stem cell transplantation for treating PD. For this purpose, we employed the Web of Science, a research database of publications and citations that are selected and evaluated by the Institute for Scientific Information in Philadelphia, PA, USA, using the key words "PD" "neural stem cells" "embryonic stem cells" "bone marrow mesenchymal stem cells" and "cell transplantation". We limited the period of publication from 2002 to 2011 and searched 1 062 results, and downloaded the data on March 20, 2012.

Inclusion criteria

The inclusion criteria were as follows: (1) peer-reviewed articles on stem cell transplantation for treating PD which were published and indexed in the Web of Science, including original research articles, reviews, meeting abstracts, proceedings papers, book chapters, editorial material, and news items; (2) the year of publication was 2002–2011; (3) the citation database was Science Citation Index-Expanded (SCI-E).

Exclusion criteria

We excluded articles that required manual searching or telephone access. We excluded documents that were not published in the public domain. We excluded a number of corrected papers from the total number of

articles analyzed.

The outcomes of all articles referring to stem cell transplantation for treating PD were measured using the following criteria: (a) type of literature on stem cell transplantation for treating PD; (b) annual publication output on stem cell transplantation for treating PD; (c) journal publications on stem cell transplantation for treating PD; (d) distribution of subject areas on stem cell transplantation for treating PD by subject area; (e) publications on stem cell transplantation for treating PD according to country; (f) publications on stem cell transplantation for treating PD by institution; (g) comparison of countries that published the most papers on stem cell transplantation from different cell sources for treating PD; (h) comparison of institutions that published the most papers on stem cell transplantation from different cell sources for treating PD; (i) comparison of study results on stem cell transplantation from different cell sources for treating PD.

RESULTS

The search results of stem cell transplantation from different cell sources for treating PD from 2002 to 2011 are presented in Table 1.

Query formulation	Number of publication
ts=("Parkinson's disease" or "Parkinson disease" or "Parkinson's" or "idiopathic parkinsonism" or "primary parkinsonism" or "paralysis agitans") and ts="stem cell"	1 062
ts=("neural stem cell" or "NSCs") and ts=("Parkinson's disease" or "Parkinson disease" or "Parkinson's" or "idiopathic parkinsonism" or "primary parkinsonism" or "paralysis agitans")	315
ts=("Parkinson's disease" or "Parkinson disease" or "Parkinson's" or "idiopathic parkinsonism" or "primary parkinsonism" or "paralysis agitans") and ts=("embryonic stem cell" or "embryonic-like stem cell" or "embryonic pluripotent stem cell" or "ESCs" or "ELSC" or "EPSC")	393
ts=("bone marrow stem cell" or "bone marrow mesenchymal stem cell" or "bone mesenchymal stem cell" or "BMSC" or "BMSCs" or "BMHSCs" or "bone marrow stromal cell") and ts=("Parkinson's disease" or "Parkinson disease" or "Parkinson's" or "idiopathic parkinsonism" or "primary parkinsonism" or "paralysis agitans")	62

The different types of publications relating to stem cell transplantation for treating PD from 2002 to 2011 are presented in Table 2.

Table 2 Types of publication on stem cell transplantation for treating Parkinson's disease included in the Web of Science from 2002 to 2011

Type of literature	Number of paper	% of total publication
Article	713	67.13
Review	248	23.35
Meeting abstract	57	5.36
Proceedings paper	54	5.08
Editorial material	29	2.73
Book chapter	12	1.13
News item	9	0.84
Correction	5	0.47
Letter	1	0.09

In Table 2, it is evident that articles, reviews, and meeting abstracts constituted the major types of publications related to stem cell transplantation for treating PD over this period. There were 713 articles accounting for 67.13% of the total number of publications, which was more than any other type of literature, followed by reviews (248) that accounted for 23.35%. The annual publication output on stem cell transplantation for treating PD from 2002 to 2011 is presented in Figure 1.

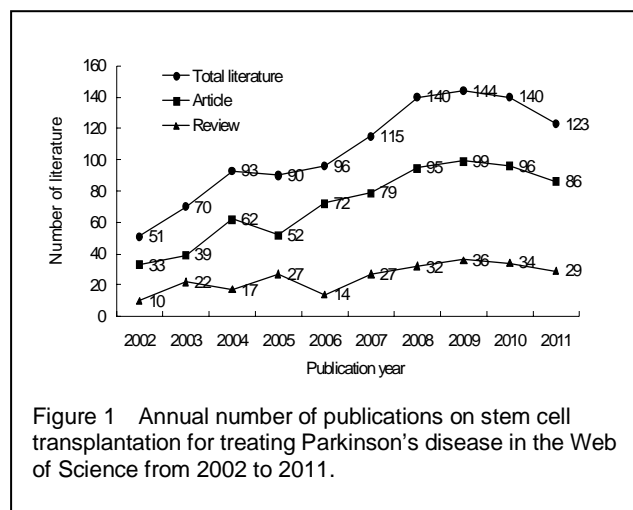


Figure 1 Annual number of publications on stem cell transplantation for treating Parkinson's disease in the Web of Science from 2002 to 2011.

There were 1 062 publications on stem cell transplantation for treating PD in the Web of Science from 2002 to 2011. The number of publications on stem cell transplantation for treating PD had gradually increased over the past 10 years. In total, 123 papers were published and included in the Web of Science in 2010, which was much more than that in 2002. However, there was a decrease in the number of papers published in 2005 and 2006.

The top 10 journals that published papers on stem cell transplantation for treating PD from 2002 to 2011 are presented in Table 3.

Table 3 Top 10 journals that published studies on stem cell transplantation for treating Parkinson's disease included in the Web of Science from 2002 to 2011

Journal	ISSN	Impact factor	Number of paper	% of total publication
<i>Stem Cells</i>	1066-5099	7.871	50	4.70
<i>Experimental Neurology</i>	0014-4886	4.436	32	3.01
<i>Cell Transplantation</i>	0963-6897	6.204	30	2.82
<i>Journal of Neurochemistry</i>	0022-3042	4.337	29	2.73
<i>Brain Research</i>	0006-8993	2.623	21	1.97
<i>Movement Disorders</i>	0885-3185	4.480	19	1.78
<i>Neuroscience Letters</i>	0304-3940	2.055	18	1.69
<i>Proceedings of the National Academy of Sciences of the United States of America</i>	0027-8424	9.771	18	1.69
<i>Stem Cells and Development</i>	1547-3287	4.791	18	1.69
<i>Journal of Neuroscience</i>	0270-6474	7.271	16	1.50

In Table 3, it is evident that most papers on stem cell transplantation for treating PD appeared in journals with a particular focus on neuroscience and stem cell research. *Stem Cells* published 50 papers that accounted for 4.70% of the total number of publications, followed by *Experimental Neurology* that published 32 papers and accounted for 3.01%.

The distribution of subject areas related to stem cell transplantation for treating PD from 2002 to 2011 is presented in Table 4.

Table 4 Distribution of subject areas related to stem cell transplantation for treating Parkinson's disease included in the Web of Science from 2002 to 2011

Subject area	Number of paper	% of total publication
Neurosciences	493	46.42
Cell biology	244	22.97
Biochemistry molecular biology	143	13.46
Research experimental medicine	119	11.20
Biotechnology applied microbiology	93	8.75
Hematology	77	7.25
Pharmacology pharmacy	68	6.40
Oncology	60	5.65
Transplantation	60	5.65
Science technology other topics	41	3.86
General internal medicine	36	3.39
Developmental biology	32	3.01
Life sciences biomedicine other topics	30	2.82

In Table 4, it is evident that among the subject categories

related to stem cell transplantation for treating PD, the greatest number of studies (493 papers) was in the field of neuroscience, which accounted for 46.42%. With 244 papers, the second highest number of studies was in the field of cell biology, which accounted for 22.97%.

The country distribution of publications on stem cell transplantation for treating PD from 2002 to 2011 according to the country is presented in Table 5.

Table 5 Top 10 countries in terms of number of studies on stem cell transplantation for treating Parkinson's disease included in the Web of Science from 2002 to 2011

Country	Number of paper	% of total publication
USA	385	36.25
Germany	105	9.88
China	91	8.56
Sweden	90	8.47
Japan	89	8.38
England	81	7.62
South Korea	54	5.08
Canada	48	4.52
Australia	39	3.67
Spain	37	3.48

In Table 5, it is clear that the United States published the highest number of papers on stem cell transplantation for treating PD. The United States published 385 papers that accounted for 36.25% of the total, which is much higher than the number of papers published by other countries. Germany ranked second with 105 papers and accounted for 9.88%.

The number of publications on stem cell transplantation for treating PD from 2002 to 2011 according to the institution is presented in Table 6.

Table 6 Top 14 institutions publishing studies on stem cell transplantation for treating Parkinson's disease in the Web of Science from 2002 to 2011

Institution	Number of paper	% of total publication
Harvard University	63	5.93
Lund University	34	3.20
Karolinska Institute	32	3.01
Kyoto University	30	2.82
University of Cambridge	20	1.88
University of Wisconsin	20	1.88
Dresden University of Technology	18	1.69
University of South Florida	18	1.69
Hanyang University	17	1.60
University of Leipzig	16	1.50
Thomas Jefferson University	14	1.31
University of British Columbia	14	1.31
Imperial College of Science, Technology and Medicine	14	1.31
Yonsei University	14	1.31

In Table 6, it is evident that the top institution for studies on stem cell transplantation for treating PD is Harvard

University, followed by Lund University and the Karolinska Institute. The comparison of countries and institutions that published the most papers on stem cell transplantation from different cell sources for treating PD from 2002 to 2011 is shown in Tables 7 and 8.

The analysis of articles on neural stem cell transplantation for treating PD from 2002 to 2011 is shown in Tables 9 and 10.

The analysis of articles on embryonic stem cell transplantation for treating PD from 2002 to 2011 is shown in Tables 11 and 12.

Table 7 Comparison of countries that published most papers on transplantation of stem cells from different sources for treating Parkinson's disease in the Web of Science from 2002 to 2011

Neural stem cells		Embryonic stem cells		Bone marrow mesenchymal stem cells	
Country	Number of publication	Country	Number of publication	Country	Number of publication
USA	85	USA	153	China	14
China	42	Sweden	47	USA	13
Germany	39	Japan	39	Japan	10
Japan	31	Germany	34	Germany	6
Sweden	25	England	32	Iran	4
England	24	China	21	Brazil	3
Canada	21	South Korea	19	England	3
South Korea	19	Australia	15	France	3
Spain	18	Italy	12	Australia	2
Australia	12	Netherlands	12	Canada	2

Table 8 Comparison of institutions that published most papers on transplantation of stem cells from different sources for treating Parkinson's disease in the Web of Science from 2002 to 2011

Neural stem cells		Embryonic stem cells		Bone marrow mesenchymal stem cells	
Institution	Number of publication	Institution	Number of publication	Institution	Number of publication
Karolinska Institutet	11	Harvard University	30	Kyoto University	6
Dresden University of Technology	11	Kyoto University	20	Capital University of Medical Sciences	3
Ajou University	10	Lund University	20	Wakayama Medical University	2
Harvard University	10	Karolinska Institutet	15	Japan Science and Technology Agency	2
University of British Columbia	10	Thomas Jefferson University	9	Johns Hopkins University	2
University of Cambridge	10	Yonsei University	9	Ludwig Maximilians University Munich	2
University of Leipzig	9	University of Wisconsin	8	Medrad Inc.	2
Lund University	7	Cornell University	7	Radboud University Nijmegen	2
Okayama University	7	RIKEN	7	University of South Carolina School of Medicine	2
Hanyang University	6	University of Cambridge	7	Shanghai Jiao Tong University	2

Table 9 Most cited articles on neural stem cell transplantation for treating Parkinson's disease in the Web of Science from 2002 to 2011

Title	Journal	Publication year	Total citation
Mechanisms and functional implications of adult neurogenesis ^[11]	<i>Cell</i>	2008	662
Evidence for neurogenesis in the adult mammalian substantia nigra ^[12]	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	2003	263
Dopamine depletion impairs precursor cell proliferation in Parkinson disease ^[13]	<i>Nature Neuroscience</i>	2004	261
The adult substantia nigra contains progenitor cells with neurogenic potential ^[14]	<i>Journal of Neuroscience</i>	2002	243
Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior ^[15]	<i>Physiological Reviews</i>	2002	194
Stem and progenitor cell-based therapy of the human central nervous system ^[16]	<i>Nature Biotechnology</i>	2005	165
No evidence for new dopaminergic neurons in the adult mammalian substantia nigra ^[17]	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	2004	119

Table 10 Studies on neural stem cell transplantation for treating Parkinson's disease

Author	Methods	Results
Lee <i>et al</i> ^[18]	Isolated neural stem cells from <i>in vitro</i> expanded mouse embryonic stem cells in medium containing bovine basic fibroblast growth factor.	After removal of the mitogen, a large number of these neural stem cells differentiated into dopaminergic neurons.
Kawasaki <i>et al</i> ^[19]	Co-culture of mouse embryonic stem cells with bone marrow-derived mesenchymal cells.	A large number of tyrosine hydroxylase-positive neurons were shown, which could produce dopamine. These neurons could survive for 2 weeks after transplantation into the mouse striatum.
Bjorklund <i>et al</i> ^[20]	Transplanted undifferentiated embryonic stem cells into animal models of Parkinson's disease induced by 6-hydroxydopamine.	The transplanted cells differentiated into cells that were similar to midbrain dopaminergic neurons. Animal models of amphetamine use showed significantly reduced amphetamine-induced rotational action. PET examinations showed a significant increase in dopaminergic biomarkers of intake behavioral change, and the transplantation area of the central blood flow increased. However, after transplantation, only a relatively small number of transplanted cells survived, and 7 out of 25 laboratory animals developed teratomas and did not survive.

Table 11 Most cited articles on embryonic stem cell transplantation for treating Parkinson's disease in the Web of Science from 2002 to 2011

Title	Publication year	Total citation
Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease ^[21]	2002	793
Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model ^[22]	2002	609
Derivation of midbrain dopamine neurons from human embryonic stem cells ^[23]	2004	379
Neural subtype specification of fertilization and nuclear transfer embryonic stem cells and application in parkinsonian mice ^[24]	2003	358
Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein ^[25]	2002	318
Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes ^[26]	2006	297
A microRNA feedback circuit in midbrain dopamine neurons ^[27]	2007	283

Table 12 Studies on embryonic stem cell transplantation for treating Parkinson's disease

Author	Methods	Results
Vescovi <i>et al</i> ^[28]	Neural stem cells derived from human embryos were transplanted into the rat striatum after passaging.	After 2 weeks, undifferentiated cells proliferated and expressed the rate-limiting enzyme tyrosine hydroxylase that performs dopamine synthesis.
Parati <i>et al</i> ^[29]	Transplantation of neural stem cells separated from the olfactory bulb into the striatum of mice suffering from Parkinson's disease.	The results showed a good therapeutic effect.
Lindvall <i>et al</i> ^[30]	In clinical trials, approximately 350 Parkinson's patients received the treatment of human embryonic brain tissue transplantation.	Transplanted neurons survived in the recipient brain and formed functional contacts. The treatment contributed to remission of clinical symptoms.

The analysis of articles on bone marrow mesenchymal stem cell transplantation for treating PD from 2002 to 2011 is shown in Tables 13 and 14.

Table 13 Most cited articles on bone marrow mesenchymal stem cell transplantation for treating Parkinson's disease in the Web of Science from 2002 to 2011

Title	Publication year	Total citation
Specific induction of neuronal cells from bone marrow stromal cells and application for autologous transplantation ^[31]	2004	286
Increased survival and migration of engrafted mesenchymal bone marrow stem cells in 6-hydroxydopamine-lesioned rodents ^[32]	2006	61
Partial recovery of dopaminergic pathway after graft of adult mesenchymal stem cells in a rat model of Parkinson's disease ^[33]	2008	38
Adult human bone marrow stromal spheres express neuronal traits <i>in vitro</i> and in a rat model of Parkinson's disease ^[34]	2006	28
From bench to bed: the potential of stem cells for the treatment of Parkinson's disease ^[35]	2008	27
Marrow stromal cells: Implications in health and disease in the nervous system ^[36]	2005	26
Treatment of neurodegenerative diseases using adult bone marrow stromal cell-derived neurons ^[37]	2005	21
Insights into autotransplantation: the unexpected discovery of specific induction systems in bone marrow stromal cells ^[38]	2006	18
Transplantation of bone marrow stromal cells containing the neurturin gene in rat model of Parkinson's disease ^[39]	2007	16
Induction of adult human bone marrow mesenchymal stromal cells into functional astrocyte-like cells: potential for restorative treatment in parkinson's disease ^[40]	2009	15

Table 14 Studies on bone marrow mesenchymal stem cell transplantation for treating Parkinson's disease

Author	Methods	Results
Yano <i>et al</i> ^[41]	Transplantation of mesenchymal stem cells expressing green fluorescent protein into the spinal cord of injured rats.	After 4 weeks, green fluorescent protein-positive cells migrated from the injection site to the dorsal white matter and expressed markers of neurons or astrocytes.
Li <i>et al</i> ^[42]	MPTP-induced Parkinson's disease mice treated with an intrastriatal injection of bone marrow stromal cells at 1 week after MPTP administration.	Transplantation of mesenchymal stem cells into the striatum reduced the motor dysfunction of the MPTP-induced mouse model of Parkinson's disease. Moreover, immunohistochemical staining showed that transplanted cells labeled with bromodeoxyuridine survived for at least 4 weeks in the brain, which demonstrated tyrosine hydroxylase activity. These observations indicated that the treatment effect may be due to generation of dopamine, and showed the feasibility and effectiveness to treat Parkinson's disease by mesenchymal stem cell transplantation.

DISCUSSION

Based on the bibliometric analysis, the following comparisons and results were obtained regarding stem cell transplantation for treating PD. First, there are 1 062 research articles addressing stem cell transplantation for treating PD included in the Web of Science from 2002 to 2011. The research on stem cell transplantation for treating PD is attracting ever-increasing attention among global researchers from 2002, notwithstanding slight drops in outputs in 2005 and 2011.

Second, subject categories including neuroscience and cell biology are involved in stem cell transplantation for treating PD. Because of this broad range, scholars and surgeons in these areas work hard and readily publish articles on stem cell transplantation for treating PD.

Third, journals focusing on neuroscience published the most articles concerning stem cell transplantation for treating PD, and *Stem Cells* has the highest total number of publications.

The most cited paper is not necessarily the highest impact paper on an annual basis. The immediate impact during the year when they were published is indicated by the average citation per annum or the citation during each year.

Much attention and effort has been devoted to stroke treatment and rehabilitation using stem cell transplantation. The findings of the present study may be of interest to fellow researchers who are currently undertaking studies on stem cell transplantation for treating PD or those who may do so in the future.

Author contributions: Runhui Li retrieved the references, extracted the data, conceived and designed the study, and wrote the manuscript.

Conflicts of interest: None declared.

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(Edited by Zhao LJ/Song LP)