Application of magnetic resonance imaging for monitoring stem cell transplantation for the treatment of cerebral ischemia*

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Abstract

OBJECTIVE: To identify global research trends in the application of MRI for monitoring stem cell transplantation using a bibliometric analysis of Web of Science.

DATA RETRIEVAL: We performed a bibliometric analysis of studies relating to the application of MRI for detecting stem cell transplantation for the treatment of cerebral ischemia using papers in Web of Science published from 2002 to 2011.

SELECTION CRITERIA: The inclusion criteria were: (a) peer-reviewed articles on the application of MRI for detecting transplanted stem cells published and indexed in Web of Science; (b) year of publication between 2002 and 2011. Exclusion criteria were: (a) articles that required manual searching or telephone access; (b) some corrected papers.

MAIN OUTCOME MEASURES: (1) Annual publication output; (2) distribution according to journals; (3) distribution according to institution; (4) distribution according to country; (5) top cited authors over the last 10 years.

RESULTS: A total of 1,498 studies related to the application of MRI for monitoring stem cell transplantation appeared in Web of Science from 2002 to 2011, almost half of which were derived from American authors and institutes. The number of studies on the application of MRI for detecting stem cell transplantation has gradually increased over the past 10 years. Most papers on this topic appeared in Magnetic Resonance in Medicine.

CONCLUSION: This analysis suggests that few experimental studies have been investigated the use of MRI for tracking SPIO-labeled human umbilical cord blood-derived mesenchymal stem cells during the treatment of cerebral ischemia.

Key Words
neural stem cells; embryonic stem cells; bone marrow mesenchymal stem cells; cell transplantation; cerebral ischemia; Web of Science; neural regeneration

Abbreviations
MSCs, mesenchymal stem cells; UCB-MSCs, umbilical cord blood-derived MSCs; SPIO, superparamagnetic iron oxide

INTRODUCTION

Cerebral ischemia is a common acute cerebrovascular disease. The key to its treatment involves the rescue of dying neurons in the ischemic penumbra and the promotion of injury recovery. Cerebral ischemia is associated with high levels of mortality and disability, and neural cell replacement therapy is the only effective treatment. Neural cell transplantation can rebuild nerve conduction loops and restore some neurological function, possibly via the differentiation of transplanted stem cells into functional glial cells or neurons, which can
thus substitute for some of the affected neurons. This replacement therapy also activates endogenous neural stem cells. The transplanted stem cells secrete cytokines to improve the local microenvironment of ischemic necrosis in terms of inflammation, tissue necrosis and glial scarring\cite{1-2}. However, cerebral ischemic damage can affect large areas and many kinds of nerve cells. Ischemic lesions may involve a number of sites in the hypothalamus, striatum, hippocampus and cortex, and reconstruction of this complex system presents a challenge for cell transplantation.

The sources of stem cells to treat cerebral ischemia include embryonic stem cells, bone marrow mesenchymal stem cells (MSCs), human umbilical cord blood (UCB) cells, human adipose mesenchymal cells, and fetal brain central nervous system cells. MSCs differ from hematopoietic stromal cells in that they are pluripotent precursor cells. UCB-derived MSCs (UCB-MSCs) have some advantages, such as strong amplification, convenience and availability, and lack of immune rejection, and they have proven a feasible and effective means of neural cell replacement therapy for cerebral ischemia\cite{3}. Transplanted stem cells show different migration and differentiation patterns under different pathological and physiological conditions in the central nervous system. These characteristics of stem cells have been investigated by sacrificing experimental animals at certain time points after transplantation. However, this invasive method does not allow the dynamic observation of the stem cells in an individual animal. Non-invasive methods are therefore required to monitor transplanted stem cells in vivo.

In 1999, Weissleder\cite{4} first proposed the concept of molecular imaging, i.e., using modern imaging techniques to carry out real-time microscopic imaging of physiological or pathological processes in vivo at a molecular level. MRI demonstrates high resolution at the molecular level and has powerful functional imaging capabilities. MRI is currently widely used for the dynamic monitoring of stem-cell migration, homing, proliferation and differentiation, and to analyze the efficacy and prognosis of stem cell transplantation in damaged zones. There is thus growing emphasis on the prospects of MRI for live-cell tracking\cite{5-6}. The contrast agent superparamagnetic iron oxide (SPIO) nanomaterial forms a core-shell structure with a dextran biopolymer coating. SPIO mainly produces a strong $T_2$-negative contrast effect. It is characterized by small particle size and strong penetrating power, with a relaxation rate of approximately 7–10 times that of gadolinium under the same conditions. SPIO can produce signal contrast in MRI at very low concentrations. It is also biodegradable with no toxic accumulation; after metabolism, it enters the normal plasma iron pool and combines with red blood cell hemoglobin, or is used in other metabolic processes\cite{7}. Some forms (such as cross-linked iron oxide particles) can also be combined with fluorescent markers to double-label stem cells, or with membrane proteins for imaging of apoptosis\cite{8}. Studies have shown that staining of SPIO magnetically-labeled cells with Prussian blue allowed the SPIO in the cells to be displayed, and the cytoplasm was shown to contain a large number of iron-containing vesicles or endosomes. Investigation of the biological activity of the labeled stem cells confirmed that the labeling had no short- or long-term toxic effects. The viability, differentiation and apoptosis rates of the labeled stem cells were unaffected compared to the unlabeled cells, and did not change over time\cite{9}. A combination of green fluorescent protein and SPIO could effectively mark neural stem cells cultured in vitro, and the proliferation and differentiation abilities of double-labeled neural stem cells were similar to those of unlabeled cells\cite{10}. Stoll et al\cite{11} used MRI to track the migration of transplanted neural stem cells labeled with ultra-magnetic iron oxide in the host brain in vivo. Chen et al\cite{12} tracked rat bone marrow-derived neural stem cells labeled with ultra-small SPIO Sinerem and transfection reagent poly-lysine complexes using MRI in vivo. Nevertheless, few experimental studies have investigated the use of MRI for tracking SPIO-labeled human UCB-MSCs during the treatment of cerebral ischemia\cite{13}.

**DATA SOURCES AND METHODOLOGY**

**Data retrieval**

Bibliometric methods were used to quantitatively and qualitatively investigate research trends in the application of MRI for monitoring stem cell transplantation for the treatment of cerebral ischemia. SCI-E is a searchable database of publications maintained by the Institute for Scientific Information in Philadelphia, PA, USA, and was used for this study. SCI-E was searched using the keywords “neural stem cells” “embryonic stem cells” “bone marrow mesenchymal stem cells” “cell transplantation” and “cerebral ischemia”. A bibliography of all articles related to the application of MRI for monitoring stem cell transplantation was compiled for the publication period 2002 to 2011.

**Inclusion criteria**

Articles closely related to the application of MRI for monitoring stem cell transplantation for the treatment of cerebral ischemia and published between 2002 and 2011 were included.
Exclusion criteria
Articles included in Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index – Science, Conference Proceedings Citation Index – Social Science & Humanities, Current Chemical Reactions, as well as Index Chemicus were excluded.

Web of Science data were performed statistical analysis using Excel. All articles referring to the application of MRI for monitoring stem cells for the treatment of cerebral ischemia that met the inclusion criteria were analyzed regarding output distribution in subject categories and journals, publication outputs of countries and institutes, and citations.

RESULTS
Search results for publications relating to the application of MRI for monitoring stem cell transplantation from 2002 to 2011 (Table 1)

| Query formulation                                                                 | Number of publication |
|----------------------------------------------------------------------------------|-----------------------|
| t5(“MRI” or “magnetic resonance imaging”) and t5(“cell transplantation” or “stem cell”) | 1,498                 |
| t5(“Superparamagnetic iron oxide” or “SPIO”) and t5(“cell transplantation” or “stem cell”) | 382                   |
| t5(“MRI” or “magnetic resonance imaging”) and t5(cerebral ischemia or brain ischemia) and t5(stem cells or cell transplantation) | 79                    |
| t5(“Superparamagnetic iron oxide” or “SPIO”) and t5(“cell transplantation” or “stem cell”) and t5(cerebral ischemia or brain ischemia) and t5(stem cells or cell transplantation) | 13                    |
| t5(MRI or magnetic resonance imaging) and t5(umbilical cord blood stem cell) and t5(umbilical cord blood stem cells) or t5(cord blood stem cell) or t5(cord blood stem cells) | 1                     |
| t5(umbilical cord blood stem cell) and t5(umbilical cord blood derived mesenchymal stem cell) or t5(umbilical cord blood derived mesenchymal stem cells) or t5(umbilical cord blood hematopoietic stem cell) or t5(umbilical cord blood hematopoietic stem cells) or t5(hematopoietic progenitor cell) or t5(hematopoietic progenitor cells) or t5(CB-SCs) or t5(UCB-MSC) or t5(UCB-MSC) |                          |

Annual publication output relating to the application of MRI for detecting transplanted stem cells from 2002 to 2011 (Figure 1)
A total of 1,498 publications relating to the application of MRI for detecting transplanted stem cells were identified in Web of Science from 2002 to 2011. The number of publications gradually increased over the past 10 years; only 27 papers were published and included in Web of Science in 2002, which was much fewer than in 2011.

Distribution of published papers relating to the application of MRI for detecting transplanted stem cells according to journal (Table 2)

| Journal                              | ISSN    | Impact factor | Number of paper | % of total publication |
|--------------------------------------|---------|---------------|-----------------|------------------------|
| Magnetic Resonance in Medicine       | 0740-3149 | 3.268         | 56              | 3.74                   |
| Circulation                          | 0009-7322 | 14.432        | 43              | 2.87                   |
| Biomaternalists                      | 0142-9612 | 7.883         | 29              | 1.94                   |
| Cell Transplantation                 | 0963-6897 | 6.204         | 23              | 1.54                   |
| Neuroimage                           | 1053-8119 | 5.937         | 23              | 1.54                   |
| Contrast Media                       | 1555-4309 | 4.020         | 21              | 1.40                   |
| Molecular Imaging & Biology          | 0142-9612 | 7.883         | 21              | 1.40                   |
| Journal of Magnetic Resonance Imaging | 1035-1807 | 2.794         | 17              | 1.14                   |
| Journal of the American College of Cardiology | 0735-1097 | 14.293 | 18              | 1.20                   |
| PLoS One                             | 1932-6203 | 4.411         | 17              | 1.14                   |
| Stem Cells                           | 1066-5099 | 7.871         | 16              | 1.07                   |
| Blood                                | 0006-4971 | 10.558        | 15              | 1.00                   |
| Bone Marrow                          | 0268-3369 | 3.660         | 15              | 1.00                   |
| Transplantation                      |          |               |                 |                        |
| European Heart Journal               | 0195-668X | 10.052        | 15              | 1.00                   |

From Table 2, it is evident that most papers relating to the application of MRI for detecting transplanted stem cells appeared in Magnetic Resonance in Medicine, which published 56 papers, accounting for 3.74% of the total number of publications; this was followed by Circulation, which published 43 papers (2.87%).

Distribution of numbers of publications relating to the application of MRI for detecting transplanted stem cells according to country (Table 3)
As seen in Table 3, most papers relating to the application of MRI for detecting transplanted stem cells were published in the USA, with 629 papers, accounting for 41.99% of the total. This output was much higher than the numbers of publications from other countries; Germany ranked second with 199 papers (13.28%) and China ranked third with 154 papers (10.28%).

### Numbers of publications relating to the application of MRI for detecting transplanted stem cells according to institution (Table 4)

In Table 4 shows that the top institution for publishing studies on the application of MRI for detecting transplanted stem cells during the period analyzed was Johns Hopkins University, followed by Stanford University.

### Distribution of publications relating to the application of MRI for detecting transplanted stem cells according to document type

Seven document types were found among the 1498 publications from 2002 to 2011. Articles (1182) were the most frequently used document type comprising 78.91%, followed by reviews (195; 13.02%), meeting abstracts (99; 6.61%), and proceedings papers (63; 4.21%). The remaining types of articles were editorial material (17), letters (5), and book chapters (1).

### Most-cited articles relating to the application of MRI for detecting transplanted stem cells (Table 5)

Seven document types were found among the 1498 publications from 2002 to 2011. Articles (1182) were the most frequently used document type comprising 78.91%, followed by reviews (195; 13.02%), meeting abstracts (99; 6.61%), and proceedings papers (63; 4.21%). The remaining types of articles were editorial material (17), letters (5), and book chapters (1).

### Table 3 Top 10 countries in terms of numbers of publications relating to the application of MRI for detecting transplanted stem cells in Web of Science from 2002 to 2011

| Country     | Number of paper | % of total publication |
|-------------|-----------------|------------------------|
| USA         | 629             | 41.99                  |
| Germany     | 199             | 13.28                  |
| China       | 154             | 10.28                  |
| Italy       | 90              | 6.01                   |
| UK          | 75              | 5.01                   |
| France      | 72              | 4.81                   |
| Japan       | 72              | 4.81                   |
| South Korea | 68              | 4.54                   |
| Canada      | 66              | 4.41                   |
| Netherlands | 64              | 4.27                   |

### Table 4 Top 12 institutions in terms of numbers of publications relating to the application of MRI for detecting transplanted stem cells in Web of Science from 2002 to 2011

| Institution                              | Number of paper | % of total publication |
|------------------------------------------|-----------------|------------------------|
| Johns Hopkins University                 | 86              | 5.74                   |
| Stanford University                      | 42              | 2.80                   |
| National Institutes of Health            | 40              | 2.67                   |
| Harvard University                       | 36              | 2.40                   |
| University of Minnesota                  | 31              | 2.07                   |
| University of California, San Francisco  | 28              | 1.87                   |
| National Heart, Lung, and Blood Institute| 26              | 1.74                   |
| University of Pennsylvania              | 25              | 1.67                   |
| Leiden University                        | 23              | 1.54                   |
| Technical University of Munich           | 21              | 1.40                   |
| University of Washington                 | 20              | 1.34                   |
| National Institute of Neurological Disorders and Stroke | 19 | 1.27 |

### Table 5 Most-cited articles relating to the application of MRI for detecting transplanted stem cells (Table 5)

| Title                                                                 | Journal                              | Publication year | Total citation |
|-----------------------------------------------------------------------|--------------------------------------|------------------|----------------|
| Intracoronary autologous bone-marrow cell transfer after myocardial   | *Lancet*                              | 2004             | 1 051          |
| infarction: the BOOST randomised controlled clinical trial[14]        |                                      |                  |                |
| Embryonic stem cells develop into functional dopaminergic neurons     | *Proceedings of the National Academy* | 2002             | 609            |
| after transplantation in a Parkinson rat model[10]                    | *of Sciences of the United States of* |                  |                |
| Intracoronary injection of mononuclear bone marrow cells in acute     | *New England Journal of Medicine*     | 2006             | 570            |
| myocardial infarction[16]                                             |                                      |                  |                |
| Transplantation of progenitor cells and regeneration enhancement in   | *Journal of the American College of*  | 2004             | 509            |
| acute myocardial infarction- Final one-year results of the TOPCARE-AMI | *Cardiology*                          |                  |                |
| trial[7]                                                              |                                      |                  |                |
| Recent advances in iron oxide nanocrystal technology for medical      | *Advanced Drug Delivery Reviews*     | 2006             | 410            |
| imaging[18]                                                           |                                      |                  |                |
| Monitoring of implanted stem cell migration in vivo: A highly resolved | *Proceedings of the National Academy* | 2002             | 389            |
| in vivo magnetic resonance imaging investigation of experimental      | *of Sciences of the United States of* |                  |                |
| stroke in rat[19]                                                     | *America*                            |                  |                |
| In vivo magnetic resonance imaging of mesenchymal stem cells in       | *Circulation*                         | 2003             | 365            |
| myocardial infarction[20]                                             |                                      |                  |                |
| Magnetic resonance tracking of dendritic cells in melanoma patients   | *Nature Biotechnology*                | 2005             | 317            |
| for monitoring of cellular therapy[21]                                |                                      |                  |                |
A total of 382 publications relating to the application of MRI for the detection of transplanted SPIO-labeled stem cells were identified in Web of Science from 2002 to 2011. The numbers of publications gradually increased over the past 10 years, apart from a slight decrease in 2010.

Distribution of published studies relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to journal (Table 6)

| Journal                               | ISSN          | Impact factor | Number of paper | % of total publication |
|---------------------------------------|---------------|---------------|-----------------|------------------------|
| Magnetic Resonance in Medicine        | 0195-668X 10.052 | 31            | 8.12            |
| Molecular Imaging and Biology         | 1536-1632 3.139 | 13            | 3.40            |
| NMR in Biomedicine                   | 0952-3480 3.064 | 13            | 3.40            |
| Radiology                             | 0033-8419 6.069 | 13            | 3.40            |
| Biomaterials                          | 0142-9612 9.076 | 12            | 3.14            |
| Contrast Media                        | 1555-4309 4.020 | 12            | 3.14            |
| Cell Transplantation                  | 0963-6897 6.204 | 9             | 2.36            |
| Journal of Magnetic Resonance Imaging | 1053-1807 2.749 | 9             | 2.36            |
| Cyttheraphy                            | 1465-3249 2.925 | 8             | 2.09            |
| Molecular Imaging                     | 1535-3508 3.169 | 8             | 2.09            |

From Table 6 shows that most papers relating to the application of MRI for detecting transplanted SPIO-labeled stem cells appeared in *Magnetic Resonance in Medicine*, which published 31 papers, accounting for 8.12% of the total number of publications; this was followed by *Molecular Imaging and Biology* and *NMR in Biomedicine and Radiology*, which published 13 papers (3.40%) each.

Distribution of publications relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to country (Figure 3)

As seen in Figure 3, the USA published the highest number of papers (173; 45.29%), followed by China (67; 17.54%) and Germany (62; 16.23%).

Distribution of published studies relating to the application of MRI for detecting transplanted SPIO-labeled stem cells according to institution (Table 7)

| Institution                          | Number of paper | % of total publication |
|--------------------------------------|-----------------|------------------------|
| Johns Hopkins University             | 45              | 11.78                  |
| National Institutes of Health        | 26              | 6.81                   |
| Stanford University                  | 20              | 5.24                   |
| University of Pennsylvania           | 11              | 2.88                   |
| Southeast University                 | 9               | 2.36                   |
| Harvard University                   | 8               | 2.09                   |
| Henry Ford Health System             | 8               | 2.09                   |
| INSERM                                | 8               | 2.09                   |
| Philips Research North America       | 8               | 2.09                   |
| Seoul National University            | 8               | 2.09                   |
| Technical University of Munich       | 8               | 2.09                   |
| University Hospital of Tübingen      | 8               | 2.09                   |
| University of Washington             | 8               | 2.09                   |
| Yonsei University                    | 8               | 2.09                   |

As seen in Table 7, Johns Hopkins University was the most productive institution in terms of studies related to the application of MRI for detecting transplanted SPIO-labeled stem cells.

Most-cited articles relating to the application of MRI for detecting transplanted SPIO-labeled stem cells (Table 8)
A total of 79 publications relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia were identified in Web of Science from 2002 to 2011. The numbers of publications showed an increasing tendency from 2002 to 2007, reached a peak in 2007, (apart from a slight decrease in 2005), then remained steady after 2007.

Distribution of published papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia according to journal (Table 9)

As seen in Table 9, most of the papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia appeared in Neuroimage, followed by Stroke and Brain Research.

Distribution of publications relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia according to country and institution

The USA published the highest number of papers (40, 50.63%). Japan ranked second (13, 16.46%), Germany ranked third (11), Sapporo Medical University, Oakland University, and Yale University were the three most productive institutions in terms of publishing papers relating to the application of MRI for detecting transplanted stem cells in the treatment of cerebral ischemia.

The most-cited papers from researchers at Sapporo Medical University from 2002 to 2011 were: BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model(23), by Kurozumi K.
et al., published in Molecular Therapy in 2004, with 125 citations.

Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat[35], by Toyama K, et al., published in Journal of Neurosurgery in 2008, with 52 citations.

Intravenous administration of glial cell line-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in the adult rat[30], by Horita Y, et al., published in Journal of Neuroscience Research in 2006, with 72 citations.

Therapeutic benefits by human mesenchymal stem cells (hMSCs) and Ang-1 gene-modified hMSCs after cerebral ischemia[31], by Onda T, et al., published in Journal of Cerebral Blood Flow and Metabolism in 2008, with 52 citations.

The most cited relevant papers from Oakland University were:

In vivo magnetic resonance imaging tracks adult neural progenitor cell targeting of brain tumor[32], by Zhang Z, et al., published in Neuroimage in 2000, with citations. Neurogenesis, angiogenesis, and MRI indices of functional recovery from stroke[33], by Chopp M, published in Stroke in 2007, with 58 citations. Effects of administration route on migration and distribution of neural progenitor cells transplanted into rats with focal cerebral ischemia, an MRI study[34], by Li L, et al., published in Journal of Cerebral Blood Flow and Metabolism in 2010, with 10 citations.

The most cited relevant papers from Yale University were:

Therapeutic benefits of angiogenic gene-modified human mesenchymal stem cells after cerebral ischemia[35], by Toyama K, et al., published in Experimental Neurology in 2009, with 31 citations. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats[36], by Omori Y, et al., published in Brain Research in 2008, with 15 citations.

DISCUSSION

The results of the current bibliometric study showed several research trends in terms of the application of MRI for monitoring stem cells transplantation. First, a total of 1,498 publications relating to the application of MRI for detecting transplanted stem cells were identified in Web of Science from 2002 to 2011, 382 of which regarding MRI for detecting transplanted SPIO-labeled stem cells and only 13 publications focus on application of MRI for detecting transplanted SPIO-labeled stem cells in the treatment of cerebral ischemia. The number of papers published annually has increased since 2002, indicating an increasing global interest in this topic over the last 10 years. Second, most relevant articles were published in Magnetic Resonance in Medicine. Finally, most articles on this topic were published in the USA. In conclusion, the USA is the most productive country in terms of research into the application of MRI for tracking the progress of stem cell transplantation, while China ranked second for publications on the use of MRI for detecting SPIO-labeled stem cells, and fourth in relation to papers on MRI for detecting transplanted stem cells in the treatment of cerebral ischemia. The findings of this study demonstrated that few experimental studies have been investigated the use of MRI for tracking SPIO-labeled human UCB-MSCs during the treatment of cerebral ischemia.

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