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Global stem cell research trend: Bibliometric analysis as a tool for mapping of trends from 1991 to 2006

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In this study, we aim to evaluate the global scientific production of stem cell research for the past 16 years and provide insights into the characteristics of the stem cell research activities and identify patterns, tendencies, or regularities that may exist in the papers. Data are based on the online version of SCI, Web of Science from 1991 to 2006. Articles referring to stem cell were assessed by many aspects including exponential fitting the trend of publication outputs during 1991–2006, distribution of source title, author keyword, and keyword plus analysis. Based on the exponential fitting the yearly publicans of the last decade, it can also be calculated that, in 2,011, the number of scientific papers on the topic of stem-cell will be twice of the number of publications in 2006. Synthetically analyzing three kinds of keywords, it can be concluded that application of stem cell transplantation technology to human disease therapy, especially research related on "embryonic stem cell" and "mesenchymal stem cell" is the orientation of all the stem cell research in the 21st century. This new bibliometric method can help relevant researchers realize the panorama of global stem cell research, and establish the further research direction.

Introduction

Stem cell science is one of the most important areas in biomedical research today. During the past decade, many promising research results indicate that stem cells, thought to be an important potential source of all types of clinically relevant cells, do bring the prospect to replace damaged tissue by the process of regeneration, ever closer to a clinical reality [THOMSON & AL., 1998; ORLIC & AL., 2001; BURD & AL., 2007]. Continuing research on stem cell has increased our understanding of some devastating human diseases like diabetes, cancer, Parkinson's disease and other neurodegenerative diseases [MARTINEZSERRANO & BJORKLUND, 1996; CAO & AL., 2002; DI GIORGIO & AL., 2007]. Despite of high growth rate, there have been few attempts at gathering systematic data on the global scientific production of stem-cell research, except for HO & AL. [2003] tried to quantitatively assess productivity of stem cell research in the Asia

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Four Dragons (Hong Kong, Singapore, South Korea, and Taiwan). A common research tool for this analysis is the bibliometric methods which have already been widely applied for the scientific production and research trends in many disciplines of science and engineering [ZITT & BASSECOULARD, 1994; TANG & THELWALL, 2003; KEISER & UTZINGER, 2005]. Furthermore, the Science Citation Index (SCI), from the Institute for Scientific Information (ISI) Web of Science databases are the most important and frequently used source database of choice for a broad review of scientific accomplishment in all studying fields [BAYER & FOLGER, 1966; BRAUN & AL., 2000].

Conventional bibliometric methods often evaluate the research trend by the publication outputs of countries, research institutes, journals, and research fields [BRAUN & AL., 1995; COLMAN & AL., 1995; UGOLINI & AL., 1997] or by the citation analysis [COLE, 1989; SCHUTZ & SIX, 1994]. However, merely depending on the change in the citations or publication counts of countries and organizations cannot completely indicate the development trend or future orientation of the research field. More information, closer to the research itself, such as source title, author keyword, keyword plus, and abstracts should be introduced in study of the research trend. ARRUE & LOPEZ [1991] evaluated the growth pattern of conservation tillage research based primarily on abstracts published in *Soils and Fertilizers*. QIN [2000] first attempted to use the keywords plus to investigate the antibiotic resistance research. The keyword plus in the SCI database supplied additional search terms extracted from the titles of articles cited by authors in their bibliographies and footnotes [GARFIELD, 1990].

In this study, we aim to synthetically use the traditional method, study field and country analysis, and the innovative method, source title, author keyword, and keyword plus analysis, mapping the trends of global stem cell research during the period of 1991–2006, which would help researchers to realize the panorama of global stem cell research, and establish the further research direction.

Data sources and methodology

The data were based on the online version of the Science Citation Index (SCI), Web of Science. SCI are multidisciplinary database of the Institute for Scientific Information (ISI), Philadelphia, USA. According to Journal Citation Reports (JCR), it indexes 6,164 major journals with citation references across 172 scientific disciplines in 2006. The online version of SCI was searched under the keyword "stem cell*" to compile a bibliography of all papers related on stem-cell research, which compromising "stem cell", "stem cells", "stem cellcontaining", "stem celltransplantation", "stem cellulose" and "stem celly". Articles originating from England, Scotland, Northern Ireland, and Wales were reclassified as being from the United Kingdom (UK). Besides, the reported impact factor (IF) of each journal was obtained from the 2006 JCR. Collaboration type was determined by the addresses of the authors, where the term "single country" was

assigned if the researchers' addresses were from the same country. The term "international collaboration" was designated to those articles that were coauthored by researchers from multiple countries.

All the articles referring to stem cell during the past 16 years, including the last 10 years of 20th century and 6 years of 21st century, were assessed by following aspects: document type and language of publications, characteristics of publication outputs during 1991–2006, distribution of output in subject categories and journals, publication outputs of country, and source title, author keyword, and keyword plus analysis.

Results and discussion

Document type and language of publication

The distribution of the document type identified by ISI was analyzed. From this study, 16 document types were found in the total 79,799 publications during the 16-year study period. As can be seen in Figure 1, articles, meeting abstracts, and reviews rose significantly, while other document types still remained in low.

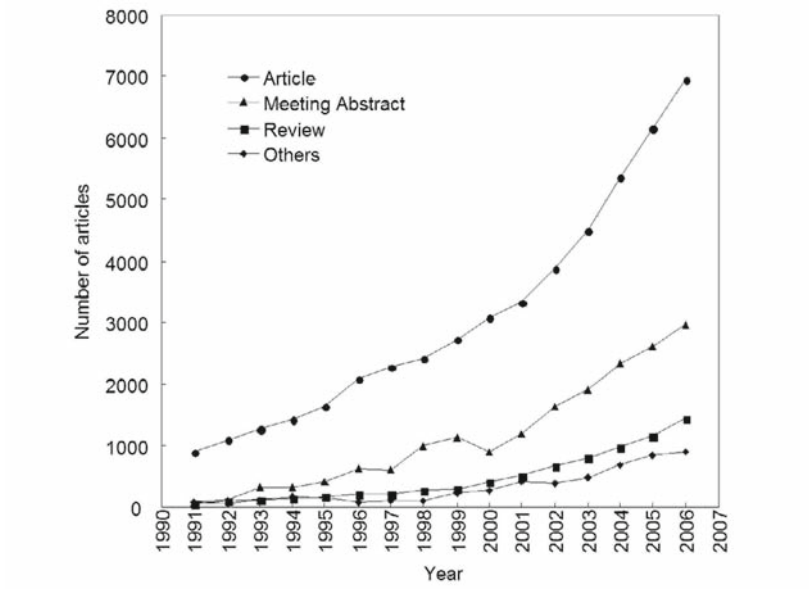

Figure 1. Pattern of the distribution of document types in the period of 1991–2006

Article (49,045) was the most-frequently used document type comprising 61% of the total production, followed by meeting abstracts (18,148; 23%), reviews (7,547; 9.5%). The others showing less significance were editorial materials (2,119), letters (1,349), new items (965), corrections (212), addition corrections (38), reprints (15), book reviews (8), discussion (6), biographical-items (5), and software review (1). Above a half of meeting abstracts were published in two core journals in stem cell research field, the *Blood* which is the journal of the American Society of Hematology and *Bone Marrow Transplantion* which is the journal of the American Society of Human Genetics.

As journal articles represented the majority of document types that were also peer-reviewed within this field. Only 49,045 original articles were used for further analysis as relevant citable items in this study, while all others were discarded. Ninety-eight percent of all these journal articles were published in English. Several other languages also appeared, containing German (357; 0.73%), French (353; 0.72%), Russian (95; 0.19%), Spanish (82; 0.17%), Chinese (37; 0.075%), Japanese (14; 0.029%), Italian (11; 0.016%), Portuguese (2; 0.0041%), Hungarian (2; 0.0041%), Javanese (1; 0.0020%), Dutch (1; 0.0020%), and Polish (1; 0.00020%).

Characteristics of publication outputs during 1991–2006

The total amounts of SCI articles including "stem cell*" in title during the last 100 years were counted and displayed in Figure 2. Along with the development of SCI, stem cell research continually grew in this long period, started to go up significantly in the year of 1991 and rocketed in the 21st century. Build on many breakthroughs in the study period during 1991–2006, especially in the recent decade, stem cell research has became one of the most important and dynamic field of human research [ROSSI & CATTANEO, 2002; CROSS & AL., 2003; ABROUS & AL., 2005].

In the last 16 years, the annual number of journal articles published and the number of articles devoted to stem cell research increased more than four-fold and seven-fold respectively, i.e., the number of articles increased from 905 in 1991 to 6,943 in 2006, with a similar increase in the number of journals (Table 1). The average article length fluctuated slightly, with an overall average length of 8.0 pages. The average number of authors per article rose from 4.4 authors per article in 1991 to 6.7 in 2006. 3.1 pertinent articles were published per journal in 1991, compared to 5.8 papers per journal in 2006, with the numbers varying through the years. The progression in the number of articles from 1991 through 2006 was further studied in Figure 3. We simulated the growth pattern by an exponential regression, while the plot of the data revealed greatly high coefficient of determinations (r^2 = 0.996) in the period 1991 to 2006.

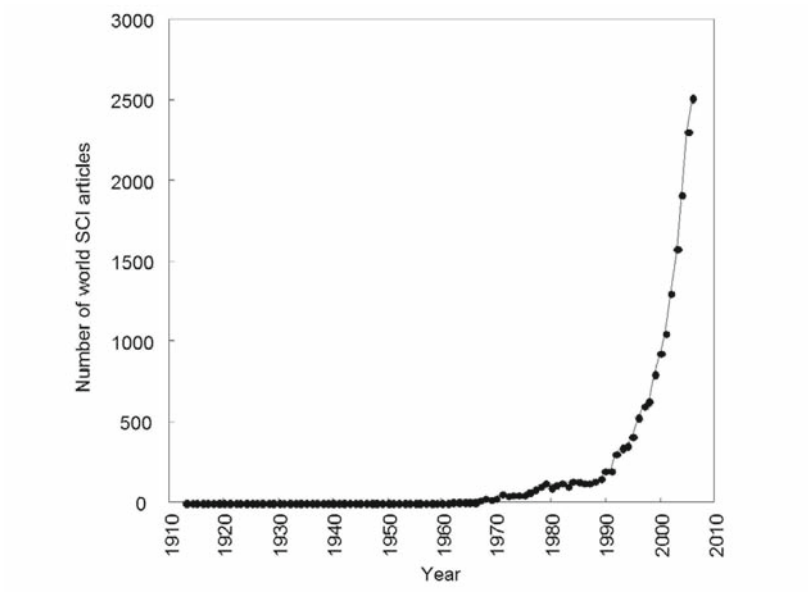

Figure 2. Number of SCI articles referring to "stem cell*" in the title during the last 100 years

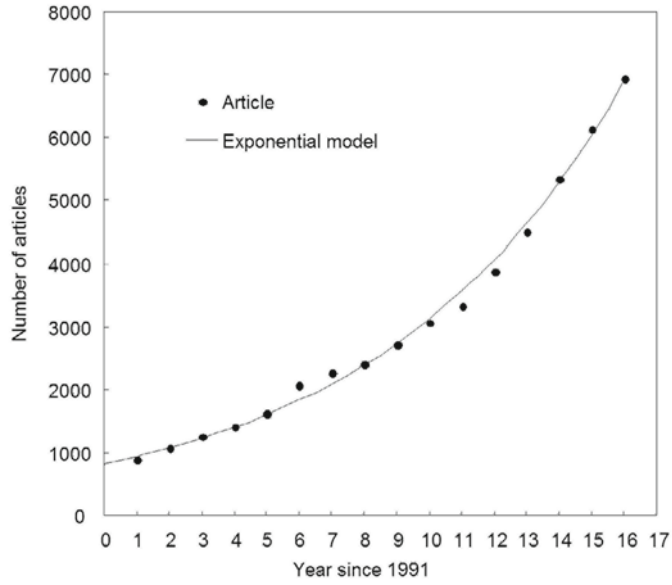

Figure 3. Cumulative number of publications by year

The relationship between the number of articles published in each year (P) and the year studied since 1991 to 2006 (Y) was found to be:

$$P = 829.1\exp(0.1325Y)$$

Based on the exponential model during 1991–2006, it can also be calculated that, in 2011, the number of scientific papers on the topic of stem cell will be twice of the number of publications in 2006.

Table 1. Characteristics by year of publication outputs from 1991 to 2006

Year	TP	PG	PG/P	NR	NR/P	AU	AU/P	J	P/J
1991	905	7,058	7.8	31,081	34	4,011	4.4	289	3.1
1992	1,089	8,250	7.6	36,467	33	5,224	4.8	307	3.5
1993	1,270	10,027	7.9	46,039	36	6,080	4.8	324	3.9
1994	1,421	11,408	8.0	49,858	35	7,292	5.1	378	3.8
1995	1,629	12,845	7.9	59,473	37	89,94	5.5	425	3.8
1996	2,080	16,398	7.9	75,887	36	11,633	5.6	484	4.3
1997	2,284	18,222	8.0	83,873	37	12,912	5.7	527	4.3
1998	2,417	19,487	8.1	90,149	37	14,454	6.0	571	4.2
1999	2,723	22,024	8.1	100,211	37	16,444	6.0	606	4.5
2000	3,070	23,986	7.8	112,950	37	18,536	6.0	660	4.7
2001	3,338	26,302	7.9	122,433	37	20,569	6.2	731	4.6
2002	3,877	30,788	7.9	143,651	37	24,094	6.2	778	5.0
2003	4,503	36,547	8.1	167,510	37	28,834	6.4	897	5.0
2004	5,351	44,640	8.3	204,723	38	34,486	6.4	970	5.5
2005	6,145	51,479	8.4	235,533	38	40,029	6.5	1,101	5.6
2006	6,943	59,784	8.6	273,315	39	46,423	6.7	1,202	5.8
Total	49,045	399,245	8.1	1,833,153	37	300,015	6.1	2,493	20

TP: Number of publications; PG: Page count; NR: Cited reference count; AU, J: Number of authors and journals; PG/P, NR/P, and AU/P: average of pages, references, and authors in a paper; P/J: average of papers in a journal.

Distribution of output in subject categories and journals

In 2006, Journal Citation Report (JCR) of the ISI contains 6,164 major journals with citation references across 172 scientific disciplines in the Science Citation Index (SCI). Based on the classification of subject categories in JCR, the publication output data of stem cell research is distributed in 167 subject categories during the last 16 years. Subject categories containing 4,000 above stem cell related articles were statistically analyzed in Figure 4. The number of scientific articles per category exhibited sustaining growth during the time period covered, which indicates that stem-cell research have been steadily developing in various categories. The three most common categories were

the hematology, oncology, and cell biology. As the use of statistics in any scientific discipline can be considered a key element in evaluating its degree of maturity [PALMER & AL., 2005], the result provided a current view of the stem cell research emphases of this topic. The hematology is holding primacy all through the last 16 years, can hardly be exceeded by other study fields. Stem cell is first found in the field of hematology, while researcher even once thought that stem cell can only apply in the hematopoietic system [SLAVIN & AL., 1998]. However, hematology is not the field with the highest growth rate and energy in recent years. At the outset of the 21st century, increasing attention was paid to the field of cell biology, while the number of stem cell related articles in cell biology went beyond the oncology for the first time in the year of 2006. The great progress of stem cell transplantation technology in the cell biology during the latest 10 years activated the flying development of this field [THOMSON & AL., 1998; KRAUSE & AL., 2001; CHAMBERS & AL., 2003].

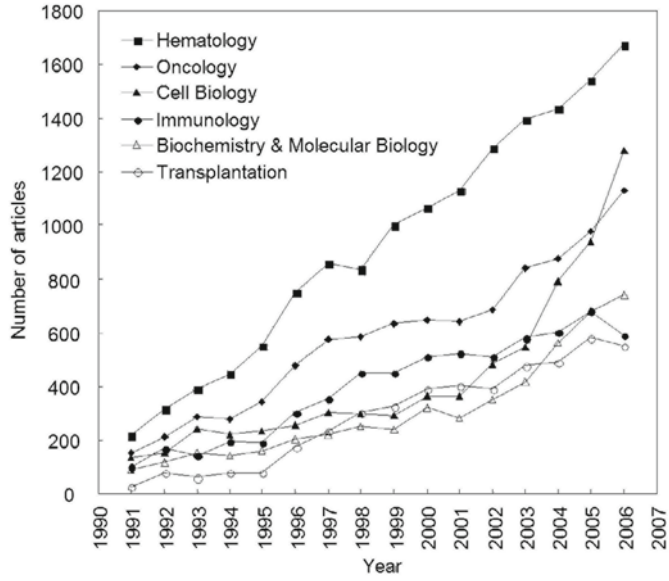

Figure 4. Comparison the growth trends of subject categories containing 4,000 above stem cell related articles during the last 16 years

In total, 49,045 articles were published in a really wide range of 2,493 journals including specialty journals, but also journals of other disciplines which all belong to 167 subject categories above. There are five journals with more than 1,000 published articles refer to stem-cell research from 1991 to 2006. Approximately 19% of the

articles reside in these 5 core journals, whereas the remainders reside in other 1,799 journals. *Blood* ranked first with 3,044 (6.2%) published papers and *Bone Marrow Transplantation* ranked second with 2,740 (5.6%) publications. These two specialty journals were holding the top 2 of all journals in the stem cell related research field during the 16-year study period.

Distribution of country publications

The contribution of different countries/territories was estimated by the location of the affiliation of at least one author of the published papers. There were 268 articles without any author address information on the ISI Web of Science. Of all the 48,777 articles with author address, 42,973 (88%) were independent publications and 5,804 (12%) were international collaborative publications. The top 15 countries/territories were ranked by number of publications, including the number and percentage of single country articles and internationally collaborated articles (Table 2).

Table 2. Top 15 most productive countries of articles during 1991–2006

Country	TP	%TP	IP	R (%)	CP	R (%)	%C
USA	20,373	42.0	17,066	1 (40)	3,307	1 (57)	16
Japan	5,847	12.0	5,057	2 (12)	790	5 (14)	14
Germany	4,799	9.8	3,443	3 (8.0)	1,356	2 (23)	28
UK	3,786	7.8	2,708	4 (6.3)	1,078	3 (19)	28
France	3,045	6.2	2,216	5 (5.2)	829	4 (14)	27
Italy	2,641	5.4	1,995	6 (4.6)	646	7 (11)	24
Canada	2,059	4.2	1,403	7 (3.3)	656	6 (11)	32
Netherlands	1,487	3.0	967	8 (2.3)	520	8 (9.0)	35
Australia	1,179	2.4	859	9 (2.0)	320	11 (5.5)	27
Sweden	1,083	2.2	678	12 (1.6)	405	10 (7.0)	37
Spain	1,031	2.1	768	10 (1.8)	263	12 (4.5)	26
China	917	1.9	720	11 (1.7)	197	15 (3.4)	21
Switzerland	881	1.8	454	15 (1.1)	427	9 (7.4)	48
South Korea	741	1.5	609	13 (1.4)	132	18 (2.3)	18
Israel	710	1.5	500	14 (1.2)	210	14 (3.6)	30

TP, total publications; IP, independent publication; CP, international collaborative publication; %TP, share in publication; %C, the percentage of international collaborative publications in total publications.

Two North American countries, nine European countries, three Asian countries, and Australia were ranked in the top 15 of publications. There are still no African or South American countries getting into the top 23 productive country. The 7 major industrial countries (G7: Canada, France, Germany, Italy, Japan, the UK, and the USA) even ranked the top 7 of world publications. Moreover, G7 had high productivity in independent papers, which included 33,888 (almost 79% of all independent papers). Domination in publication was not surprising from mainstream countries since this pattern has occurred in most scientific fields [MELA & AL., 1999]. To a certain extent,

the number of research papers reflected the activity and academic level of these countries were likewise high [ARUNACHALAM & JINANDRA, 2000; TRAJTENBERG, 2001]. Since the earliest stem-cell research occurred in these industrial countries, they conducted the earliest and the most relative research performances. The USA showed the greatest counts of world publications, followed distantly by other countries.

It also had the most-frequent partners accounting for 57% of all the international collaborative articles during the last 16 years, but comparing to its total publications, the USA presented a very low percentage (16%) of collaboration with outside authors.

Although the USA exhibited its predominant in global stem cell research, it can be clearly seen in Figure 5 that the publications share of the USA distinctly decreased in our study period, especially in the latest decade. The global trend of stem cell research is accordant with the developmental trends toward world multipolarization and scientific research globalization, while other countries in the world were gradually reducing their disparities with the USA. The time-trend analysis among other 6 major industry countries was displayed in Figure 6. An obvious rise can been seen in the number of articles related to stem cell research of all six countries, while the rapid development of global stem cell research in the last 16 years was partly driven by these countries' contribution [CARMELIET & AL., 1996; HIROTA & AL., 1998; YING & AL., 2002]. Japan has the highest growth pace in recent 10 years, with the lowest share (14%) of international collaborative articles in its total publications among the top15 productive countries, which represents its powerful independence in stem cell related research field. In 2000, Japanese government released a report to endorse the use of human stem cells in research-work that had been on hold in a long period.

The draft report outlines a process for both publicly and privately funded scientists to follow in deriving and working with stem cells [DENNIS, 2000]. There is no doubt that a series of positive policies motivate the rapid development of the stem cell research in Japan. Another significantly increasing point is Germany, which was keeping ahead of other countries in the Europe during the last decade. On the other hand, the percentage of publications from Canada, France and UK in the period of 1991–2006 was slightly reduced, which indicates that the growth pace of stem cell research in these three countries is much slower than other productive countries. However, it must be pointed out that the slowness could be attributed to various factors, while stem cell research itself refers to science, religion, ethic and politics. Many in society object to using stem cells derived from human embryos, and debates never vanish a second in the progress of stem cell research [FRANK, 2000]. To some extents, the policy, including the law and regulation in these countries could be a decisive cause restricting the progress of stem cell research [GUENIN, 2005].

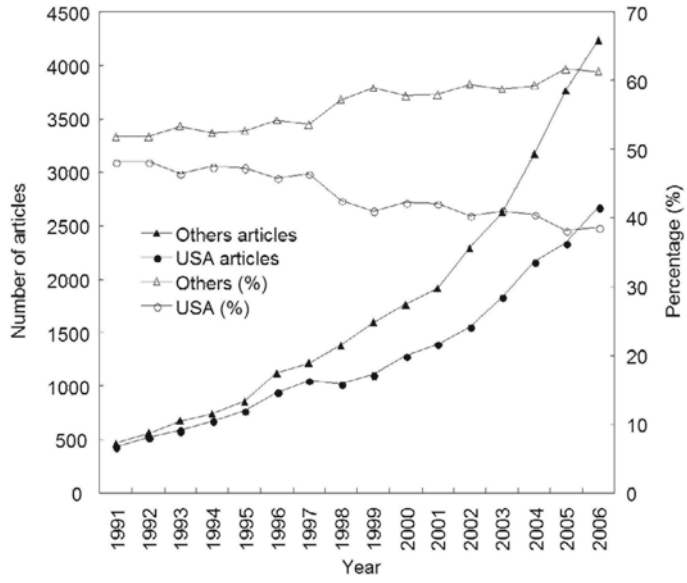

Figure 5. Comparison the growth trends of the USA and all other articles in the world in number and percentage during the last 16 years

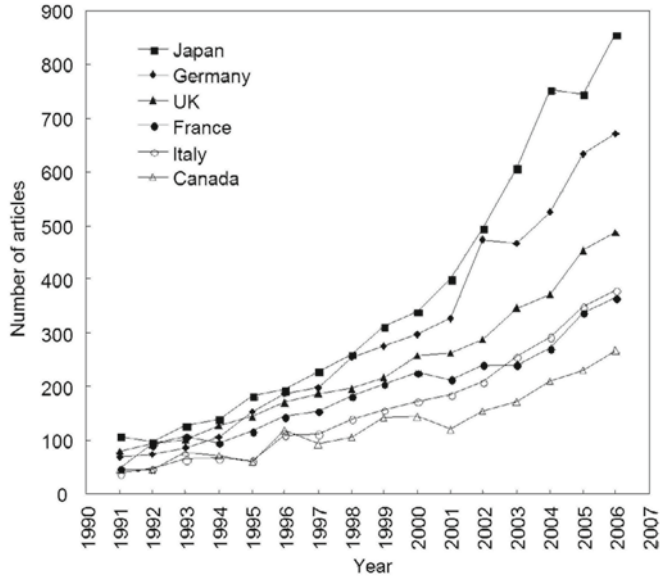

Figure 6. Comparison the growth trends of other 6 major industry countries' articles during the last 16 years

Distribution of source title analysis

RODRÍGUEZ & MOREIRO [1996] primarily assess the growth and development of research by the dissertation title analysis. They used the length and key words per title to compare the complexity of title between countries. The title of an article always includes the information which author would most like to express to their readers, because it would be seen by all the readers at first. In this study, we have statistically analyzed all the single words in the title of stem cell related articles. Some prepositions such as "of" (41,562) and "in" (28,555), apparently are used frequently during our study period, however, these are no useful meaning for the analysis of research trend. Therefore, all these empty words including "of", "in", "and", "the", "a", "for", "with", "by" etc. were discarded in analysis of the Table 3. For the further study, after eliminating 14 empty words above, 25 most frequently used single words in title, which are all substantives, have been analyzed in Table 3 through past 16 years, and also in 4 four-year periods respectively. Along with the growth of the number of articles, almost all the number of single words increased in the study period.

Table 3. Top 25 most frequency substantives in the title of articles during 1991–2006 and 4 four-year periods.

Word in title	91–06		91–94		95–98		99–02		03–06	
	TP	(%)	TP	(%)	TP	(%)	TP	(%)	TP	(%)
Cells	18,479	(38)	1,768	(38)	3,200	(38)	4,495	(35)	9,016	(39)
Cell	17,337	(35)	1,476	(32)	2,967	(35)	4,839	(37)	8,055	(35)
Stem	16,507	(34)	1,228	(26)	2,261	(27)	4,252	(33)	8,766	(38)
Transplantation	7,363	(15)	384	(8.0)	1,026	(12)	2,333	(18)	3,620	(16)
Human	6,949	(14)	775	(17)	1,202	(14)	1,666	(13)	3,306	(14)
Hematopoietic	5,360	(11)	774	(17)	1,063	(13)	1,423	(11)	2,100	(9.2)
Bone	5,182	(11)	587	(13)	938	(11)	1,301	(10)	2,356	(10)
Marrow	5,134	(10)	688	(15)	1,052	(13)	1,346	(10)	2,048	(8.9)
Blood	4,830	(9.8)	464	(9.9)	1,219	(14)	1,618	(12)	1,529	(6.7)
Factor	3,984	(8.1)	672	(14)	1,031	(12)	994	(7.6)	1,287	(5.6)
Expression	3,949	(8.1)	453	(9.7)	731	(8.7)	1,042	(8)	1,723	(7.5)
Gene	3,864	(7.9)	542	(12)	886	(11)	1,008	(7.7)	1,428	(6.2)
Patients	3,456	(7.0)	169	(3.6)	590	(7)	1,113	(8.6)	1,584	(6.9)
Differentiation	3,263	(6.7)	312	(6.7)	491	(5.8)	734	(5.6)	1,726	(7.5)
Progenitor	3,028	(6.2)	265	(5.7)	713	(8.5)	777	(6)	1,273	(5.5)
Embryonic	2,863	(5.8)	211	(4.5)	361	(4.3)	507	(3.9)	1,784	(7.8)
Peripheral	2,853	(5.8)	296	(6.3)	814	(9.7)	976	(7.5)	767	(3.3)
Mouse	2,794	(5.7)	374	(8.0)	508	(6.0)	644	(5.0)	1,268	(5.5)
Mice	2,644	(5.4)	429	(9.2)	658	(7.8)	707	(5.4)	850	(3.7)
Autologous	2,470	(5.0)	217	(4.6)	490	(5.8)	812	(6.2)	951	(4.1)
Leukemia	2,325	(4.7)	327	(7.0)	427	(5.1)	643	(4.9)	928	(4)
High	2,304	(4.7)	195	(4.2)	489	(5.8)	798	(6.1)	822	(3.6)
Growth	2,291	(4.7)	359	(7.7)	558	(6.6)	540	(4.2)	834	(3.6)
Allogeneic	2,285	(4.7)	38	(0.8)	284	(3.4)	756	(5.8)	1,207	(5.3)
Derived	2,170	(4.4)	97	(2.1)	229	(2.7)	453	(3.5)	1,391	(6.1)

TP: the number of articles in the study period; %: the percentage of the Source Title.

"Transplantation", "human" and "hematopoietic" were emphasis of stem-cell research in the sixteen-year study period, which indicates the application of stem cell transplantation technology and hematopoietic stem cell in human were always the mainstream issue in the research field. The words "patient" and "disease" more frequently appeared in the Title, while the percentage of articles with these two words increased from 3.6% and 2.1% to 6.9% and 4.4%. Once researchers recognized the extraordinary potential of stem cells, immature cells with the ability to become different kinds of tissue-and perhaps to heal many kinds of illness, they attempted to use the stem cell to treat human diseases in all sorts of ways [GRETCHEN, 1999; ORLIC & AL., 2001]. Besides that, some words such as "embryoic", "allogeneic" and "derived" have an apparently higher growth rate than any other words, and are more frequently used in recent periods. Taking the "allogeneic" as an example, the number and percentage of articles related on stem cell research with "allogeneic" in the title went up from 38, 0.8% in 1991–1994 to 1207, 5.3% in 2003–2006, which are highly accorded with great attention given to allogeneic stem cell transplantation in recent decade [SLAVIN & AL., 1998; BENSINGER & AL., 2001]. On the other hands, the percentage of some words such as "blood", "autologus", "peripheral", "Leukemia", "gene" and "growth" obviously reduced respectively. There are two possible explanations for these decreases. For one thing, some of them are the general words in stem cell research which are replaced by more specific or definite single words in the title of articles. "Blood" and "gene" might belong to this case. Another possible explanation is that some title words are gradually disregarded by researchers, or are retreated from the mainstream of stem cell research. For example, earlier stem cell application focused to Leukemia, as one of various diseases of the bone marrow. It is concerned with the primal understand about the function of stem cell. However, since researchers found that stem cells could be the source of all types of clinically relevant cells not only hematopoietic cell, they tired to use stem cells to treat many other human diseases, such as lymphoma (being studied in 1,136 articles), myeloma (927), acute or chronic damaged liver (789) and brain (706), which ultimately brought on the appearance frequency of "leukemia" declined in the last 16 years [ATTAL & AL., 1996; SLAVIN & AL., 1998; WANG & AL., 2003].

Distribution of author keyword analysis

The source titles and author keywords supply "reasonably" details of the articles" subject. Especially, author keyword analysis could offer the information of research trend which is concerned by researchers. Bibliometric method concerning author keyword analysis can only be found in recently years [CHIU & HO, 2007], whereas using the author keyword to analyze the trend of research is much more infrequent [HO, 2007]. The technique of statistical analysis of keywords might be aimed at discovering directions of science, and prove important for monitoring development of science and

programs. Examination of author keywords in this study period revealed that 40,229 author keywords were used. Among them, 28,465 keywords appeared only once, and 4,721 keywords appeared twice. The large number of once-only author keywords probably indicated a lack of continuity in research and a wide disparity in research focuses [CHUANG & AL., 2007]. Most of the research articles were not considered to be mainstream stem-cell research by their authors. Author keywords appeared in the articles refer on stem cell from 1991 to 2006 were calculated and ranked by total 16-year study and 4 year-time periods. Author keywords that appeared more than 400 times in all in last 16 years are displayed in Table 4, while research changes can be roughly found. Except for "stem cell" and "stem cells" which were searching keywords in this study, the two most frequently used keywords were "differentiation" and "transplantation". These two words are also the basis of all stem cell research in the world, while "differentiation" is the elementary function of stem cell, and "transplantation" is radical technology of stem cell research [ORLIC & AL., 2001].

Table 4. Top 25 frequency of author keywords used

Author keywords	91–06	91–94	95–98	99–02	03–06
	TP (%)	R (%)	R (%)	R (%)	R (%)
Stem cells	2,040 (6.8)	1 (7.4)	1 (6.0)	1 (5.8)	1 (7.5)
Differentiation	1,313 (4.4)	3 (4.3)	6 (2.9)	3 (3.4)	2 (5.3)
Transplantation	1,135 (3.8)	12 (2.0)	7 (2.8)	2 (3.8)	3 (4.3)
Stem cell	1,041 (3.5)	11 (2.4)	8 (2.8)	4 (3.4)	4 (3.9)
Stem cell transplantation	792 (2.6)	154 (0.33)	22 (1.7)	5 (3.3)	5 (2.9)
Hematopoiesis	766 (2.6)	2 (7.0)	2 (4.1)	8 (2.4)	19 (1.5)
Bone marrow transplantation	696 (2.3)	6 (3.0)	4 (3.4)	6 (3.2)	22 (1.4)
Apoptosis	646 (2.2)	75 (0.57)	13 (2.2)	9 (2.3)	8 (2.3)
Embryonic stem cells	644 (2.1)	9 (2.7)	18 (1.9)	17 (1.6)	7 (2.4)
Bone marrow	642 (2.1)	10 (2.5)	12 (2.3)	10 (2.1)	10 (2.1)
Gene therapy	599 (2.0)	17 (1.6)	14 (2.2)	7 (2.5)	14 (1.8)
Mouse	580 (1.9)	13 (2.0)	15 (2.2)	12 (2.0)	11 (1.8)
Hematopoietic stem cells	532 (1.8)	4 (3.8)	16 (2.1)	14 (1.7)	23 (1.4)
Neurogenesis	512 (1.7)	99 (0.47)	47 (0.86)	16 (1.7)	9 (2.2)
Multiple myeloma	481 (1.6)	53 (0.76)	24 (1.7)	13 (1.9)	18 (1.6)
Stem cell factor	460 (1.5)	7 (3.0)	3 (3.4)	15 (1.7)	62 (0.64)
Mesenchymal stem cells	450 (1.5)	1,139 (0.047)	2,283 (0.021)	73 (0.6)	6 (2.6)
Hematopoietic stem cell transplantation	425 (1.4)	583 (0.095)	59 (0.69)	19 (1.5)	13 (1.8)
Proliferation	419 (1.4)	27 (1.2)	32 (1.2)	30 (1.1)	15 (1.6)
Cytokines	412 (1.4)	8 (2.8)	9 (2.6)	21 (1.4)	42 (0.8)
CD34	402 (1.3)	17 (1.6)	5 (3.0)	21 (1.4)	47 (0.77)
High-dose chemotherapy	397 (1.3)	53 (0.76)	19 (1.8)	11 (2.0)	36 (0.89)
Chemotherapy	375 (1.2)	36 (1.0)	20 (1.8)	20 (1.4)	32 (1.0)
G-CSF	352 (1.2)	19 (1.4)	11 (2.4)	21 (1.4)	62 (0.64)
Stem cells	2,040 (6.8)	1 (7.4)	1 (6.0)	1 (5.8)	1 (7.5)

TP: publications in the study period; R (%): the rank and percentage of the author keyword

Different from segmenting the title into single words in source title analysis, in this section, we preserved the intact words that the authors want to transmit to the readers. The same single word or phrase therefore can be seen in different author keywords. For instance, of all the 40,495 stem-cell-related articles in the last 16-years, there are more than 6,631 (16%) articles referring "transplantation", comprising "transplantation" (1,135), "stem cell transplantation" (792), "bone marrow transplantation" (696), "hematopoietic stem cell transplantation" (425), "autologous stem cell transplantation" (333), "allogeneic stem cell transplantation" (269), and other 673 different author keywords with the single word "transplantation". Large amounts of promising research progresses make various transplantation technologies in stem cell application research increasingly absorbing to researchers [SLAVIN & AL., 1998; MARR & AL., 2002]. Besides, in the past 16 years, especially the latest decade, "embryonic stem cells" and "mesenchymal stem cells" had extremely high increasing rate in ranking of all the author keywords in the study period. Since the epoch-making article "embryonic stem cell lines derived from human blastocysts' written by Thomson et al. was published in *Science* in 1998, human embryonic stem cells immediately found to be the most flexible stem cells for genetic engineering, which are also an optimal choice as a cell source for cell-replacement therapy [HYNES & ROSENTHAL, 2000]. Similarly, the rank and percentage of "mesenchymal stem cell" and "mesenchymal stem cells" as its plural form change from "4745th, 0%", "1139th, 0.04%" in 1991–1994 to "27th, 1.2%", "6th, 2.6%" in 2003–2006. It indicates, apparently, that mesenchymal stem cell attracted extensive attentions during the latest 4 years. Indeed, mesenchymal stem cells, which can be purified and culture-expanded from animals and humans, have been shown to successfully regenerate functional tissue when delivered to the site of musculoskeletal defects in experimental animals [BRUDER & AL., 1998; LIECHTY & AL., 2000]. It can be promisingly applied in the treatment of many tissue diseases such as renal failure [GUPTA & AL., 2002]. All through the study period, "multiple myeloma" (used as author keyword in 481 articles) is the most frequently used author keywords concerned with diseases. Followed by "graft-versus-host disease" (330), "leukemia" (317), and "breast cancer" (287) etc. Increasing understand of stem cell by global researchers will exploit its extraordinary potential to suggest therapeutic strategies that eventually could benefit patients with issue failure diseases [GRETCHEN, 1999]. Not until 1995, researchers got started to use "tissue engineering" as author keyword in their articles. It was once thought that tissue-specific stem cells could only differentiate into cells of the tissue of origin; however, subsequent studies suggested that tissue-specific stem cells can differentiate into lineages other than the original tissue [JIANG & AL., 2002]. Although most studies did not conclusively demonstrate that a single tissue-specific stem cell differentiate into functional cells of multiple tissues, tissue engineering still became the popular topic in the field of stem cell research in 21st century. On the contrary, a decline in the ranking of the keyword "hematopoiesis", "stem cell factor", "cytokines",

"CD34", and "G-CSF" was visible. The decrease of "stem cell factor" might attribute to the reason mentioned above that some more specific or definite words replace this general word. The word "cytokines" containing "G-CSF" (granulocyte colony-stimulating factor) promotes mobilization of stem cells from bone marrow to the peripheral blood. "CD34" is the earliest found differentiation marker of hematopoietic stem cells, which could be expressed on human and mouse hematopoietic stem cells and used as an important marker for isolating the hematopoietic stem and progenitor cells [KRAUSE & AL., 2001]. The decline in the ranking and percentage of these words in stem cell research field is attributed to the related lower growth pace than other similar words. We may make a conjecture that these gradually declining trends will be continue in the future stem cell research field.

In order to further study the global trends on stem cell research, we try to make a comparison between "hematopoietic stem cell", "embryonic stem cell", and "mesenchymal stem cell" during the period of 1991–2006. All author keywords referring to "hematopoietic stem cell" (HSC), "embryonic stem cell" (ESC), and "mesenchymal stem cell" (MSC) are statistically analyzed in Figure 7.

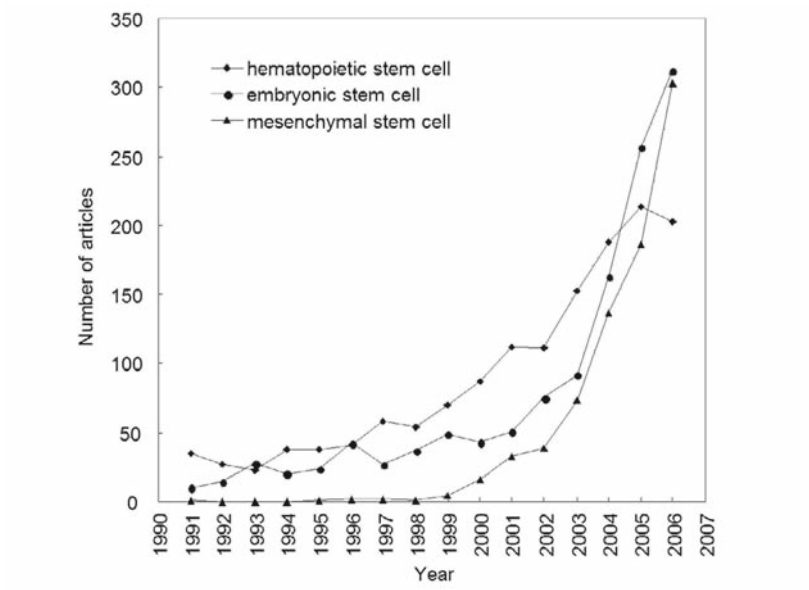

Figure 7. Comparison the trends of "hematopoietic stem cell", "mesenchymal stem cell", and "embryonic stem cell" during the period of 1991–2006

"Hematopoietic stem cell" is first found in the bone marrow of adults, and has the ability to give rise to any of the end-stage blood cell types [CHERVENI & BOGGS, 1969;

LAGASSE & AL., 2000]. As the pioneer human stem cell, HSC research has been always keeping ahead in the stem cell related research until 2005. "Embryonic stem cell" is first extracted from mice's embryo in 1891, and professor Thomson's group at University of Wisconsin is successfully derived the embryonic stem cell lines from human blastocysts in 1998 [THOMSON & AL., 1998]. After this big breakthrough on human ESC research, ESC related publications rapidly increased, even being close to the number of articles related on the HSC in 1999, and ultimately exceeding the HSC, became dominant in stem cell research in 2006. The research of human "mesenchymal stem cell", the same as HSC which was also derived from the bone marrow, began apparently later than the HSC and MSC, however, has rocketed in 21st century [LI & AL., 2002]. During the passed two years, the number of articles related on MSC has the highest growth pace and successfully transcend the HSC in 2006 (Figure 4). It can be concluded that, research in the stem cell topic related on "embryonic stem cell" and "mesenchymal stem cell" application to human disease therapy will undoubtedly maintain the hotspots of stem research in the future.

Distribution of keyword plus analysis

Keywords plus provides search terms extracted from the titles of papers cited in each new article in the database in ISI [GARFIELD, 1990]. In source title analysis, as we segment the title into single word, the result is no repeated and can be statistically analyzed by rule and line; however it breaks the integrality of phrase in title. While in author keywords analysis, we preserve the intact words that the authors want to transmit. Although it makes same single word or phrase appear in different author keywords, we can compare discrimination between author keywords, or sum up the dissimilar keywords with common phrase or single word for further study. The keyword plus analysis as an independent supplement, reveals the articles contents with more details. There are some similar and dissimilar trends between their statistical results in this study periods. The distribution of the keywords plus with its rank and percentage in different periods was revealed in Table 5. Same as the author keywords rank, some words, e.g., "differentiation", "bone-marrow transplantation", "transplantation", "hematopoietic stem-cells", "proliferation", and "mouse" were also emphases of keywords plus in the study period. However, except "differentiation" and "transplantation", almost all other words represent low growth rate or even decrease in the recent years. The decrease of these words might be due to the gradual maturity of these orientations in stem cell research. Keywords plus as an additional search terms, are usually more concerned about the novel research direction than the mature direction in the field [GARFIELD, 1990]. Through the keyword plus analyzing in Table 5, it can be seen that more attention was given to "in-vitro" and "in-vivo" in our study period. In-vitro experiments of stem cells, together with animal implant studies, are always the

basic study method in the stem cell research, while many startling research results are found in these experiments [THOMSON & AL., 1998; PITTENGER & AL., 1999; JIANG & AL., 2002]. Almost no "in-vitro" and "in-vivo" appeared in keyword plus before 1994, the explanation is that these two single words are substitutes of "invitro" which was used as keyword plus frequently before 1994 (5th, 11%). The distinct decrease in used "invitro" can be clearly seen along with the increasingly used of "in-vitro" and "in-vivo" during the last 16 years. The rank of many other keywords plus do not fluctuate clearly in study periods which shows that the development of stem cell research is basically steady and concentration in the past 16 years [FENSTERMACHER, 2007].

Table 5. Top 25 frequency of keywords plus used

Keywords Plus	91–06	91–94	95–98	99–02	03–06
	TP (%)	R (%)	R (%)	R (%)	R (%)
Stem-cells	8,350 (17)	1 (21)	1 (19)	2 (16)	1 (17)
Expression	7,698 (16)	2 (17)	2 (18)	3 (15)	2 (16)
Differentiation	5,352 (11)	3 (12)	5 (9.6)	6 (8.9)	3 (13)
In-vitro	4,447 (9.3)	510 (0.23)	16 (5.0)	4 (10)	4 (12)
Progenitor cells	4,426 (9.3)	10 (7.2)	6 (9.4)	5 (9.3)	5 (9.6)
Bone-marrow transplantation	4,310 (9.0)	12 (6.8)	4 (11)	1 (17)	19 (4.0)
Bone-marrow	3,854 (8.1)	8 (8.3)	7 (8.5)	7 (8.3)	7 (7.7)
Transplantation	3,244 (6.8)	15 (4.7)	9 (6.7)	10 (6.6)	9 (7.3)
Colony-stimulating factor	3,174 (6.6)	4 (12)	3 (13)	9 (7.2)	22 (3.2)
Mice	3,102 (6.5)	11 (7.1)	10 (6.6)	11 (6.5)	10 (6.3)
Hematopoietic stem-cells	2,904 (6.1)	6 (9.7)	8 (7.5)	13 (5.8)	13 (5.0)
In-vivo	2,851 (6.0)	1433 (0.068)	36 (2.5)	8 (7.4)	8 (7.6)
Therapy	2,432 (5.1)	22 (3.7)	17 (4.8)	12 (5.9)	14 (5.0)
Proliferation	2,286 (4.8)	9 (7.4)	13 (5.7)	21 (3.7)	17 (4.5)
Gene	2,221 (4.6)	14 (5.2)	12 (5.9)	15 (4.7)	18 (4.1)
Embryonic stem-cells	2,172 (4.5)	19 (4.2)	18 (4.8)	19 (4.1)	16 (4.7)
Bone-marrow-transplantation	2,128 (4.4)	3130 (0.023)	581 (0.21)	346 (0.35)	6 (9.1)
Stem-cell transplantation	2,059 (4.3)	181 (0.66)	55 (1.8)	17 (4.4)	11 (5.9)
Mouse	1,989 (4.2)	7 (8.6)	14 (5.5)	23 (3.4)	23 (3.2)
Gene-expression	1,968 (4.1)	48 (2.2)	31 (2.8)	25 (3.4)	12 (5.4)
Peripheral-blood	1,802 (3.8)	36 (2.6)	15 (5.4)	14 (5.2)	34 (2.6)
Chemotherapy	1,758 (3.7)	23 (3.6)	19 (4.8)	16 (4.5)	29 (2.8)
Central-nervous-system	1,746 (3.6)	219 (0.57)	73 (1.4)	18 (4.2)	15 (4.7)
Growth	1,698 (3.5)	15 (4.7)	22 (3.7)	28 (3.0)	20 (3.6)
Growth-factor	1,678 (3.5)	13 (6.4)	20 (4.4)	24 (3.4)	30 (2.7)

TP: publications in the study period; R (%): the rank and percentage of the keyword plus

Conclusion

In this study on stem cell papers dealing with SCI, we obtained some significant points on the research performance throughout the period from 1991 to 2006. The exponential model fitting showed that yearly publicans had a distinct growth with a high rate during the last decade. There were totally 2,493 journals listed in the 167

subject category. The mainstream research on stem cell was in hematology, oncology, and cell biology fields, while increasing attention was paid to the field of cell biology in 21st century. As the flagship journal of the field, *Blood* published the most articles. The G7, which had a longer tradition in research in this field, held the majority of total world production. It was notable that the USA, contributing the most independent and international collaborative articles, had the most-frequent partners but presented a very low percentage of collaboration with outside authors. The law and regulation in each country could be a decisive factor to the progress of stem cell research. By synthetically analyzing the distribution and change of source title, author keywords and keyword plus, we describe the development of research on stem cell during last decade, and predict the future orientation of stem cell research. It can be concluded that application of stem cell transplantation technology to human disease therapy, especially research related on "embryonic stem cell" and "mesenchymal stem cell" are the orientation of all the stem cell research in the 21st century. The result analysis by this new bibliometric method can help relevant researchers realize the panorama of global stem cell research, and establish the further research direction.

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