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Global competencies of regional stem cell research: bibliometrics for investigating and forecasting research trends

We employed a bibliometric approach to examine regional stem cell research in the USA, the UK, Japan and China based on publications from 2007 to 2011 with a co-citation clustering analysis to identify region-specific clusters of global competencies. We observed that there are clear differences in the number and interdisciplinary spread of competencies across regions: the USA retains the largest capacity and capability for pursuing medical and pharmaceutical applications; China has shown substantial growth through fusion approaches with chemistry and material sciences; Japan has been pursuing basic biology and is currently seeking further growth; and the UK has shown considerable growth and quality with a focus on medical research and the widest interdisciplinary spread. Furthermore, we discuss policy implications from these results in terms of industrial and clinical applications. These findings provide a rational way of evaluating research policies and forecasting research trends.

KEYWORDS: management of technology ▪ research and development strategy ▪ research policy ▪ scientometrics ▪ stem cell ▪ technology forecasting

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The field of stem cell research has grown rapidly, particularly since the beginning of the 21st century; it is now extending to incorporate other areas of the sciences [1,2]. For instance, medicinal and synthetic chemistry have provided a number of small molecules that are useful for the selective control of stem cell proliferation and differentiation [3]. As another example, numerous trials of various medical applications have been undertaken to determine how to design synthetic materials in order to emulate the microenvironment in which stem cells reside [4]. Furthermore, beyond the natural sciences, areas such as computing (including bioinformatics), humanities (such as bioethics), social sciences (such as the management of technology) and policy science are increasingly involved in interdisciplinary or multidisciplinary research activities. There is an expectation that stem cell research will yield future medical and pharmaceutical advances, and governments and both public and private organizations have made substantial investments to facilitate innovative research [5,6]. As the field diversifies, governments are increasingly expected and required to articulate effective research strategies at the academic, policy and industry levels. Because of these characteristics, we focus on the stem cell field as a good case for investigating the trend of interdisciplinary research spread and evaluating the management of innovation and policies.

One approach for investigating research trends through bibliometric analysis is to classify publications into categories according to a predefined taxonomy, such as cell species, origin of the cells (human or mouse, among others), research phase (basic, applied or translational, among others) or field of the scientific journals in which the studies were published. This approach is beneficial for investigating whether the observer has set criteria based on a clear hypothesis to be investigated [7,8]. However, this approach has a critical weakness in the context of exploring the frontiers of interdisciplinary research fields that have developed in unexpected directions.

An alternative approach to scanning research trends relies on methods of clustering scientific publications. There are two common ways to cluster documents: similarity or deconstruction and assignment. The similarity approach calculates direct similarities between pairs of documents. If one is using common entries in bibliographies to compare two documents, the method is called bibliographic coupling [9]. In this approach, text-mining techniques are often adopted to determine similarities between documents using fields such as authors, keywords and words in titles and abstracts. The similarity approach is widely used by established services such as Google™ Scholar and PubMed; however, ambiguity in wording must be resolved, and a large amount of computation is required for these processes.

Deconstruction and assignment is an alternative approach to the clustering method. Co-citation analysis is an example of this approach

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that uses the references of each publication [10]. This is a multistep process that goes as follows: identification of the publications cited in references; calculation of how many times pairs of cited publications have coexisted in the identical citing publication; clustering of cited publications using a transform of the co-occurrence matrix; and assigning the remaining publications to these clusters. Co-citation analysis enables the observer to identify research fields independent of predefined categories, which means that the observer can detect newly established fields of interdisciplinary research in a systematic way [11]. Furthermore, this method incorporates publications that are linked to the field of interest through citations and by identification using a given keyword.

Better understanding of research trends from both global and regional perspectives contributes to the design of effective policies and research strategies at the governmental, institutional and individual levels. However, for the aforementioned reasons, there are limited opportunities to systematically and holistically review recent interdisciplinary developments in stem cell research. In this study, we examine these trends using a bibliometric co-citation analytical approach, which has been applied to the field of regenerative medicine [12] and stem cell research [13]. We selected four countries as case examples: the USA, which has been leading stem cell research, particularly through clinical translation; mainland China, an example of an emerging country that has become involved through the regional expansion of stem cell research; Japan, which is renowned for its basic sciences and recent discoveries such as induced pluripotent stem (iPS) cells; and the UK, which has considerable experience in creating innovation infrastructure for cell banking and technology standardization [14].

Methods & data

In order to investigate the growth and characteristics of the stem cell research fields in these four regions, we adopted SciVerse Scopus™ (Elsevier) as the publication database for the coverage of journal titles and SciVal Spotlight™ (Elsevier) as the analytical tool because of its compatibility with the publication database, as proven in a previous study [13].

SciVerse Scopus has filed 20,469 active journal titles (as of 14 February 2013), of which 530 titles (2.6%) were from publishers in China and 420 titles (2.1%) were from publishers in Japan (manufacturer's instructions). These journals from China and Japan may include publications written in local languages; however, Scopus indexes only references written using the Roman alphabet. Search results indicated that 412,772 out of 532,158 (77%) publications published in China and 131,537 out of 168,902 (77%) publications published in Japan between the years 2007 and 2011 included references on Scopus. The database generally completes its data population of the prior year at approximately May of each year; thus, the dataset used for this study ensures representation of a complete collection of recent publications.

The SciVal Spotlight applies a co-citation clustering analysis according to the deconstruction and assignment method as described earlier to all publications listed in the SciVerse Scopus that also have references. To begin, publications with 4–100 citations published in 2011, as defined by the SciVerse Scopus database, were selected. Then, the remaining publications were supplied to each of the initial pools by using the co-citation method to form a cluster of publications. The number of clusters nominated for each country was then defined based on the relative article share of the country with the largest publication output (the USA in this case). The selected clusters for each country were then grouped as being strong in the region (hereinafter competencies).

The constituent publications of competencies were selected through the following keyword search method. In both publication databases, this study simply applied 'stem cell' to a search string. For publications covered by Embase and/or Medline, Scopus adds Emtree/MeSH keywords to the original author keywords. The Emtree hierarchy was studied to confirm that 'stem cell' was used as the preferred term as of 1978, meaning any publication with 'stem cell' as its major focus topics will include this keyword within Scopus.

Major disciplines of the publications correspond to the following categorization method of journals. The SciVal Spotlight assigns 554 journal categories based on a bibliographic coupling analysis of approximately 16,000 journals using both references and keywords [15]. Journal categories are named based on the names of the journals in each category. The taxonomy used is provided by the Elsevier Fingerprint Engine™, which uses natural language processing techniques combined with unique thesaurus support to leverage the intellectual value of the thesauri (manufacturer's instructions). The Elsevier Fingerprint Engine mines the unstructured text of scientific documents and publication abstracts specifically for the database to create an index of weighted terms that defines the text.

For each competency, the growth rate was defined by the publication rate between 2007 and 2011, and the number of citations (or citation counts) was defined as the sum of the citations of the constituent publications.

The Derwent Innovations Index (Thomson Reuters) was employed as the source to measure innovations in stem cell-related sectors for patent-based analysis. The Derwent Innovations Index covers more than 14.3 million basic inventions from 40 patent-issuing authorities worldwide, and it is considered an appropriate index for innovations. We set the number of patents applied for as the innovation measure rather than those granted for the following reasons: it is difficult to obtain the number of patents granted across multiple countries with different standards; there is bias when patents granted by different countries are compared because they are influenced by law, policy and culture, and so on; it is not consistent in the case that a patent has been approved in one country but not in others; and, as with clinical trials, the activities for innovation, rather than the results, are discussed herein.

We retrieved 15,159 records of patent families, which may be identified by several patent numbers in different patent offices, on 15 August 2012, using the following algorithm: Topic = ('stem cell*'), Time span = '1963–2011' and Databases = 'CDerwent, EDerwent, MDerwent'. Second, we used the keywords 'stem.*cell', indicating the coexistence of 'stem' and 'cell(s)' in a keyword, to capture the different expressions of 'stem cell' in the list of keywords extracted from the title and abstract and identify stem cell-related patents through an established protocol [16]. Finally, 10,853 records of stem cell-related patent families were identified.

For the clinical trial-based analysis, we extracted data relevant to stem cells from the ClinicalTrials.gov database (as of 5 January 2013), a service of the US NIH. Here, we applied 'stem cell' as a search string to all the available sources in terms of the type of recruitment (open and closed), the availability of study results (with results or without) and the type of study (interventional, observational and expanded access). Finally, we obtained 2692 records for these four regions and classified them by country according to the protocol defined using the database. It should be noted that the data source has such limited international data that non-US clinical trials may be underestimated, and that registered and unregistered clinical studies that have been widely demonstrated in Japan are excluded for consistency with other countries and because of the unavailability of datasets.

Results of bibliometric analysis

We compiled a universal record of publications in the USA, China, Japan and the UK between 2007 and 2011 (FIGURE 1A) and compared this data with all publications that included the term 'stem cell' (FIGURE 1B). Stem cell science and technology have been rapidly growing in recent years with breakthrough events, such as inventions of human iPS cells in 2007 and the first clinical trial using human embryonic stem cells in 2010, as well as the geographical expansion of research and development. Therefore, we determined the observation period to these 5 years due to these being relatively new areas of research and also the applicability of the co-citation clustering methods. The number of publications related to stem cells has increased steadily during this period, and it was higher than the average growth rate of all scientific fields. Specifically, the 5-year compound annual growth rate of stem cell publications was 12.1% and that of all scientific fields was 4.4%. The USA produced 33–38% of all stem cell-related publications annually throughout this period. Notably, China's contribution over this period grew substantially, possibly as a result of vigorous public investment and infrastructure development.

We then applied a worldwide co-citation clustering analysis to all accessible publications in order to understand the recent research trends in these four regions. Using this approach, we identified specific sets of competencies (114, 26, 14 and 12 competencies in the USA, China, Japan and the UK, respectively). We distributed these competencies according to the growth rate and number of citations per publication of a competency, and we calculated simple and weighted averages across all competencies in each region (FIGURE 2).

The average growth rates of these competencies in the UK, the USA, China and Japan were 6.5, 5.7, 3.6 and 1.1%, respectively. Here, both the UK and the USA showed significantly higher growth rates for stem cell research than did China ($p < 0.05$) and Japan ($p < 0.05$), implying that, in both regions, the focus was on growing stem cell research or establishing new fields therein.

The average citation counts of these competencies in the USA, the UK, Japan and China were 12.1, 11.2, 7.5 and 3.7, respectively. These values for stem cell research in the USA and the UK were significantly higher than those in China ($p < 0.05$) and Japan ($p < 0.05$).

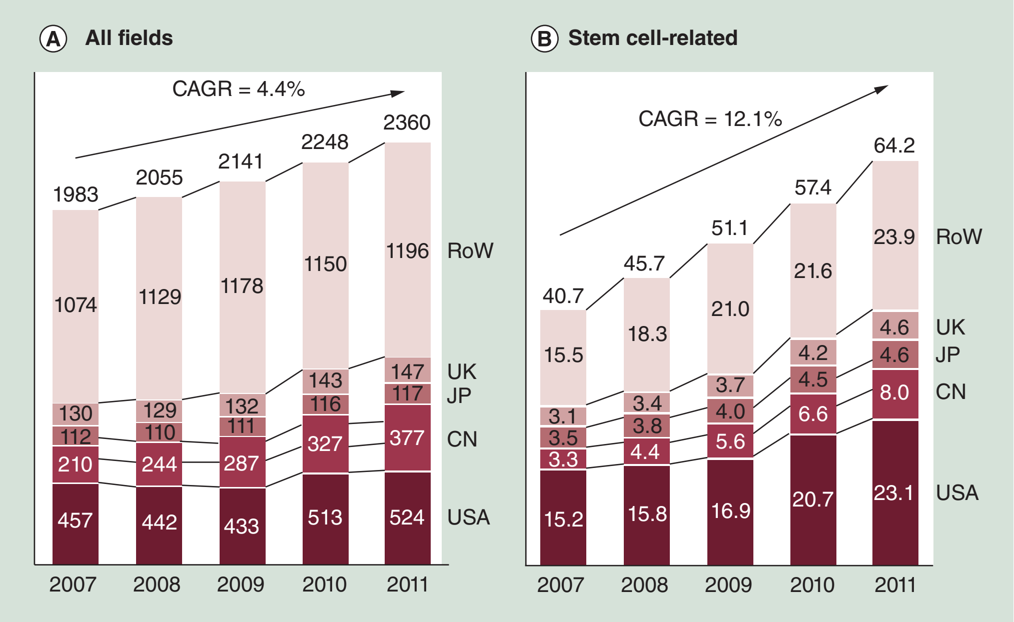

Figure 1. Growth of publications and citations relevant to stem cell research. The numbers of publications (in thousands) in **(A)** all fields and **(B)** stem cell-related fields between 2007 and 2011 are presented. Publications containing the term 'stem cell' in their title, abstract or keywords are classified by region into the USA, CN, JP, the UK and the RoW. The 5-year CAGR values for the numbers of publications are shown above these graphs.
CAGR: Compound annual growth rate; CN: China; JP: Japan; RoW: Rest of the world.

We then selected several competencies and investigated their contents and regional characteristics. The three fastest-growing competencies in the USA were as follows: metabolism of cancer cells (annual growth of 35.3%, 14.0 citation count; Figure 2A); embryonic stem cells and iPS cells (32.1%, 21.3; Figure 2B); and miRNAs (27.3%, 22.1; Figure 2C). Notably, these competencies are characterized by high citation counts. Other growing competencies were related to radiation and hematopoietic stem cells (annual growth of 19.6%, 7.6 citation count; Figure 2D) and morals and ethics in social science (15.1%, 2.5; Figure 2E). In China, there were no specifically high-citation competencies, but there were relatively fast-growing competencies. These were related to cartilage tissue engineering (annual growth of 13.2%, 4.9 citation count; Figure 2F), cancer stem cells (12.4%, 4.8; Figure 2G), dental pulp and regeneration (11.7%, 3.8; Figure 2H), polymers and plastics (11.3%, 4.0; Figure 2I), regeneration in peripheral nerves (10.0%, 2.8; Figure 2J), mesenchymal stem cells and clinical transplantation (9.9%, 4.4; Figure 2K) and drug discovery (9.1%, 4.1; Figure 2L). In Japan, a large competency with modest growth and relatively high citations per publication (annual growth of 1.1%, 8.2 citation count; Figure 2M) was observed in the field of cell biology of germline development, such as oocytes, embryonic structure, spermatozoa and blastocysts. Japan also had a fast-growing, modest citation competency in the field of dentistry (annual growth of 8.7%, 7.0 citation count; Figure 2N); moreover, the competency with the highest growth rate but a low citation rate was related to posterior leukoencephalopathy syndrome (a newly recognized brain disorder; 12.1%, 1.6; Figure 2O). In the UK, there were two distinctively high-performing competencies (Figure 2P & 2Q). These were in the fields of telomeres and aging (annual growth of 14.0%, 12.5 citation count; Figure 2P) and plant science and chemistry (11.5%, 15.6; Figure 2Q). Fast-growing competencies with modest citation counts were observed in the fields of Raman spectrum analytical chemistry (annual growth of 14.3%, 8.2 citation count; Figure 2R) and deliberative democracy in social science (10.1%, 4.4; Figure 2S).

Furthermore, we holistically examined the research subjects and disciplines of competencies by region and found clear differences between the regions based on regional publication share (Figure 3). We counted publications related to stem cell competencies by research subject and discipline, and we calculated the proportional share of each subject and discipline. In terms of subjects, medicine, biochemistry, genetics and molecular biology comprised a high proportion of shares across all four regions (Figure 3A). In terms of disciplines, the most common research fields in these regions were cell biology (the USA: 28.6%; China: 23.6%; Japan: 38.2%; and the UK: 12.9%) and general medicine (the USA: 11.4%; China: 8.8%; Japan: 14.0%; and the UK: 16.3%; Figure 3B). We also observed some differences between the regions in terms of trends and characteristics. In the USA, medicine, biochemistry,

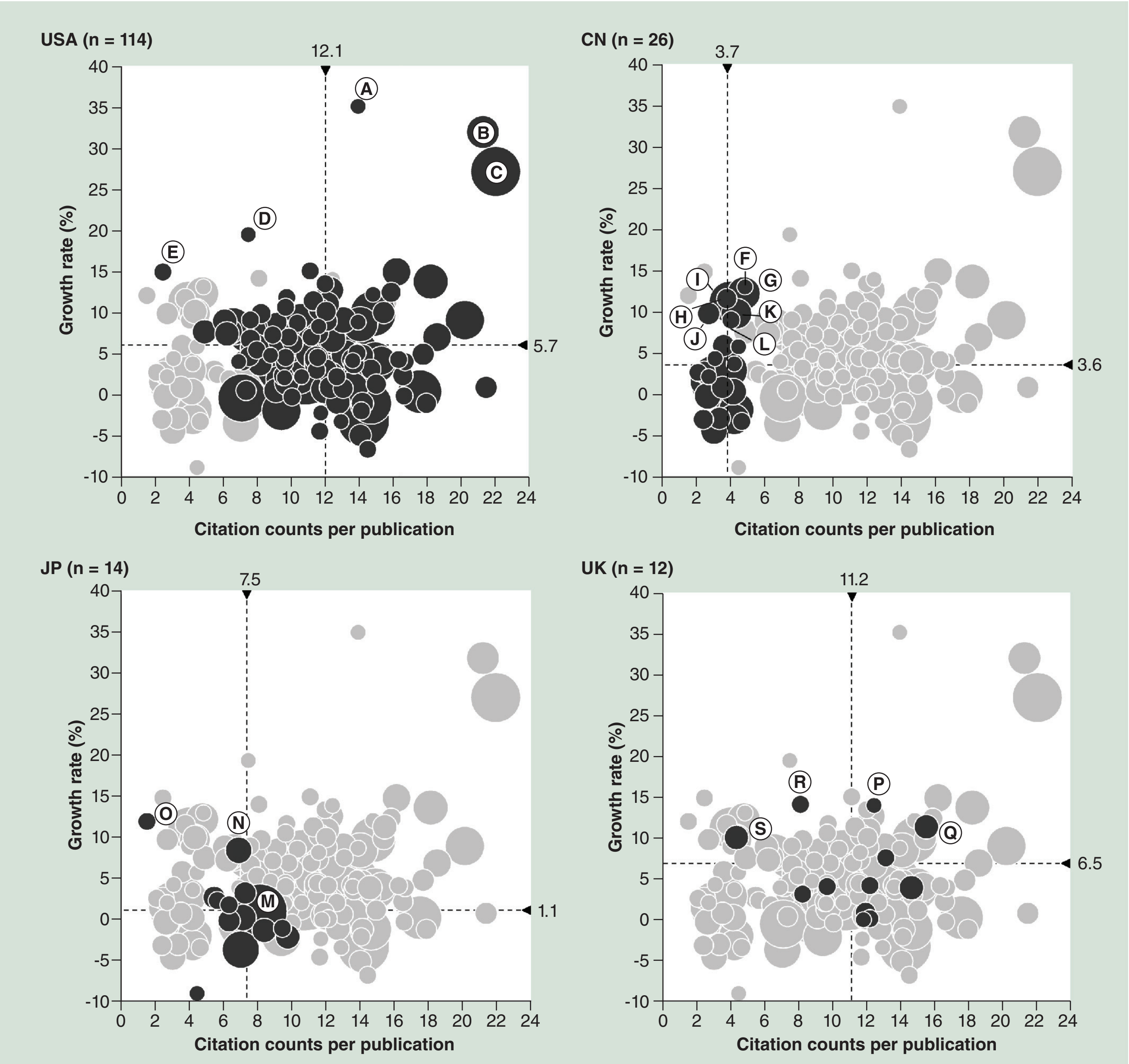

Figure 2. Regional stem cell competencies by growth rate and citations per publication. Stem cell-related competencies of the USA, CN, JP and the UK (dark circles) are individually plotted against those in the other countries (light circles) in a matrix with citations per publication (x-axis) and growth rate (y-axis), where the circle size represents the number of relative publications for each competency. All items are fractionized if a publication contributes to multiple competencies. The weighted averages by the numbers of publications are shown in each region with a dotted line for average growth rates or citations per publication. **(A–S)** Representative competencies: **(A)** metabolism of cancer cells; **(B)** embryonic stem cells and induced pluripotent stem cells; **(C)** miRNAs; **(D)** radiation and hematopoietic stem cells; **(E)** morals and ethics in social science; **(F)** cartilage tissue engineering; **(G)** cancer stem cells; **(H)** dental pulp and regeneration; **(I)** polymers and plastics; **(J)** regeneration in peripheral nerves; **(K)** mesenchymal stem cells and clinical transplantation; **(L)** drug discovery; **(M)** biology of germline development; **(N)** dentistry; **(O)** posterior leukoencephalopathy syndrome; **(P)** telomeres and aging; **(Q)** plant science and chemistry; **(R)** Raman spectrum analytical chemistry; and **(S)** deliberative democracy in social science.
CN: China; JP: Japan.

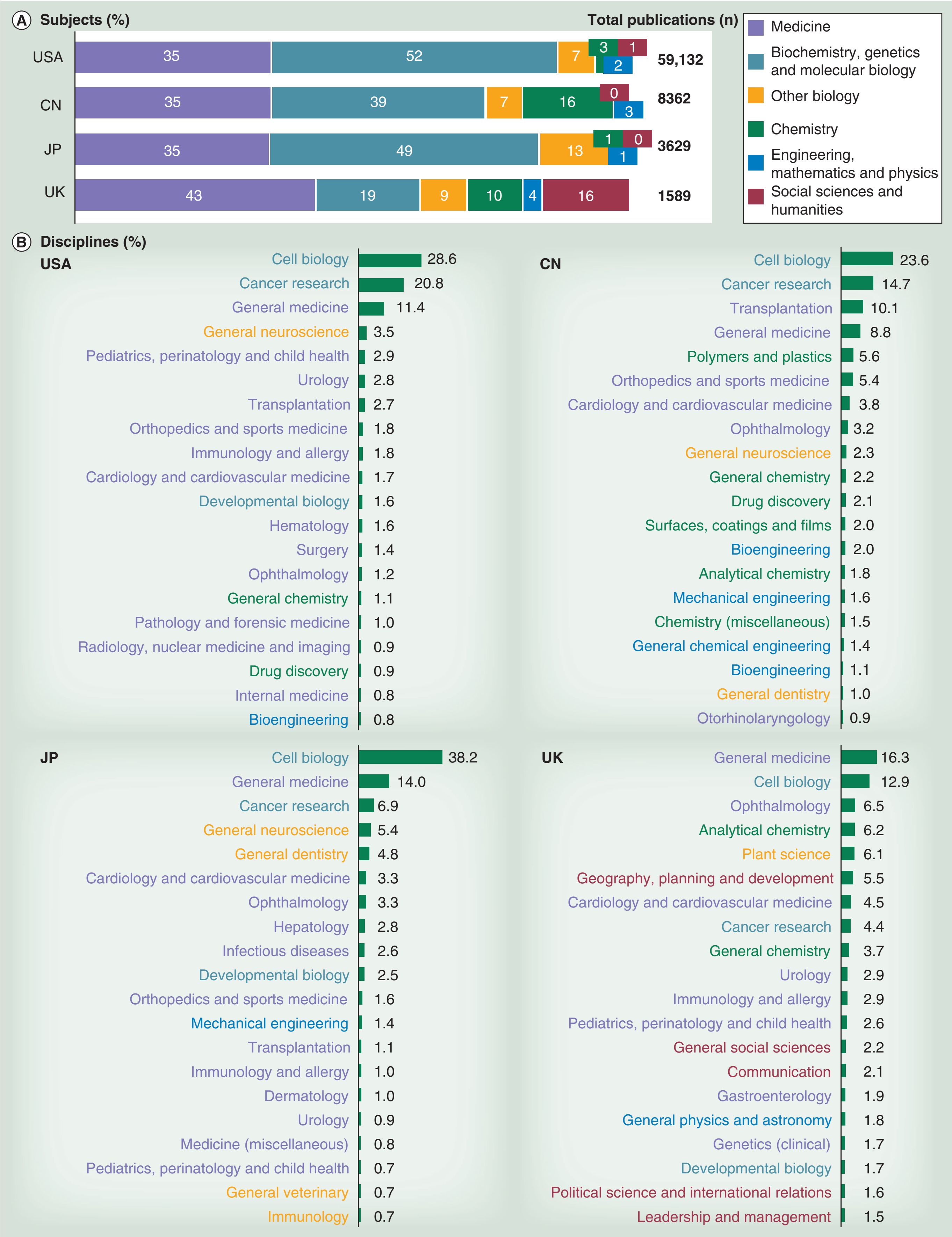

Figure 3. Regional characteristics of research subjects and disciplines of stem cell research (continued on next page)**.**

Figure 3. Regional characteristics of research subjects and disciplines of stem cell research (facing page). The subjects and disciplines that competencies fall into are allocated to the USA, CN, JP and the UK based on given classifications. The shares of subjects and disciplines are defined according to the number of publications. **(A)** Research subjects are categorized into six domains as indicated by the different colors, and the publication share of each domain is shown. **(B)** The publication shares of the top 20 research disciplines of each country are shown; their domains are shown in the same six colors as in **(A)**.
CN: China; JP: Japan.

genetics and molecular biology had the largest share of publications (FIGURE 3A). Notably, as in the competency-based observation, cancer-related research in a broader context, which might include research on the mechanisms of pluripotency or cancer stem cells, had the highest share among the four regions (FIGURE 3B). In China, stem cell research was more focused on chemistry- and engineering-related research – for example, polymers and plastics (5.6%), drug discovery (2.1%) and surfaces, coatings and films (2.0%) – coupled with a high share for transplantation (10.1%). In Japan, the distribution of subjects and dominant disciplines was similar to that in the USA. However, the shares of interdisciplinary fields such as chemistry, engineering and sociology were smaller in Japan. By contrast, cell biology had a large share (38.2%) within the Japanese competencies compared with the other countries. The UK is distinct in the nature of its interdisciplinary research. The shares of social sciences and humanities such as geography, planning and development, and communications were larger than those of other regions. At the same time, the shares of the top disciplines (general medicine: 16.3%; cell biology: 12.9%; and ophthalmology: 6.5%) were relatively small (FIGURE 3B).

Implications for the innovation process

From the holistic view of the overall innovation process, research activities represented in publications are apical elements, and these seeds of innovation grow into final products and services through development and commercialization phases. In particular, clinical development and approval processes are essential when aiming for therapeutic applications. In order to verify our results, we investigated whether the intensity and spread of research performance correlates positively with the downstream innovation process. Our investigation focused on two indicators: patent applications and clinical trials. The number of patent applications and the number of clinical trials related to stem cells were extracted from the relevant databases and compiled and compared across the regions, along with the publication data (FIGURE 4).

The USA topped the field of stem cell research in terms of the number of publications in 2007–2011 (91,700), patent applications to date (4203 patent families) and clinical trials to date (2436 registered projects). As discussed, the USA had the highest share of and the most rapid growth rate in stem cell-related publications during the observed period (FIGURE 1B). The USA also has high levels of competency in medical research and basic cell biology (FIGURES 2 & 3). This indicates that the USA has an advantage in the overall innovation process and, in particular, boasts an overwhelmingly large number of clinical trial projects. Notably, the NIH supplied approximately US$968 million of funding in 2007 for stem cell research, and this figure dramatically increased to reach approximately US$1.2 billion in 2011 [17,101]. Furthermore, state-level funding was also vital in the observed period [18]. These facts support the notion that the observed competencies oriented towards clinical applications grew rapidly (FIGURE 2), and attest to the richness of the research in the field of medicine (FIGURE 3).

China had 27,800 publications, 871 patent applications and 107 clinical trials recorded in the observed period. The volume of publications on stem cell-related research has recently grown rapidly (FIGURE 1), and the overall characteristics of the competencies indicate an emphasis on interdisciplinary research across chemistry and engineering and towards clinical applications (FIGURE 2). For instance, the Chinese government established a project named ‘Program 863’ in 2011 to investigate stem cell and human tissue engineering [102]. Such policy initiatives seem to have effectively leveraged China’s original strengths with respect to their focus on medical applications given the high capital efficiency of research activities and the progress in clinical trials and patent applications (FIGURE 4).

Japan had 20,400 publications, 1526 patent applications and 32 clinical trials recorded in the observed period. Japan has relative historical strength in the fields of basic biology and medical research (FIGURE 2); a major portion of the public funding for stem cell research has been allocated to fundamental or basic research (FIGURE 3B) [19]. Comparatively, interdisciplinary

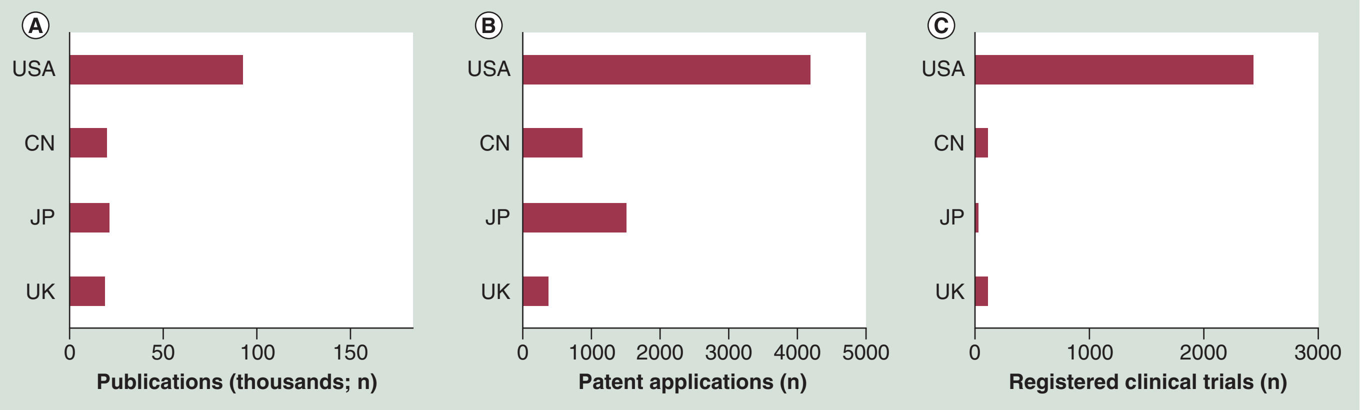

Figure 4. Country comparison of scientific research and industrial and clinical applications. A comparison between the USA, CN, JP and the UK for **(A)** the number of publications, **(B)** the number of patent applications and **(C)** the number of clinical trial projects. Here, the number of publications is the cumulative value for the years 2007–2011 (Figure 1B), the number of patent applications is the cumulative value of the patent family base until 2012 and the number of clinical trial projects is the cumulative value based on the number of applications registered (see the 'Results of bibliometric analysis' section for details).
CN: China; JP: Japan.

development, such as that in the UK, has been limited in Japan (Figure 3A), which may explain why Japan's citation counts remain lower (Figure 2). This result is consistent with a previous study that investigated the by-country trend of average citations for the case of pluripotent stem cell research [20]. Notably, Japan continues to have the lowest number of clinical trials (Figure 4), although Japan has performed clinical studies that are not counted in the international database. This evidence suggests that innovation trajectories are not fully oriented to clinical applications, despite Japan's implementation of top-down initiatives through, in particular, the Project for the Realization of Regenerative Medicine for research aimed at producing visible results [103].

In the UK, 19,000 publications, 383 patent applications and 117 clinical trials were reported in the observed period. We presume that the UK's remarkably competitive citation count compared with that of the USA accounts for its higher ratio of international studies [17]. Our study suggests another possibility: that the UK's wider interdisciplinary spread has formed a basis for pioneering studies, which may lead to higher citation counts. We assume that this interdisciplinary trend originates from the UK's encouragement of public engagement. The Medical Research Council (MRC), the major public funding agency for biomedical research, has been promoting dialog with the public concerning the clinical application of stem cell technologies, particularly human embryonic stem cells, and nearly 60% of the researchers receiving MRC funding were enrolled between 2006 and 2009 [104]. As a precedent and a related example, the Human Fertilisation and Embryonic Authority (HFEA) is dedicated to providing impartial and authoritative information to the public in accordance with its mandate to manage fertility clinics and studies using human embryos in the UK [105]. This supportive evidence suggests that the UK has cleared the way for interdisciplinary activities, especially with the social sciences and humanities, which might explain its relatively competitive performance in terms of clinical applications of stem cells, although further bibliometric investigation is required to prove the generality of this observed tendency.

The co-citation analysis makes use of direct relationships among research publications to develop an outline of interdisciplinary research; this is different from previous approaches, in which the assigned category has usually been defined by the journal in which the study was published. On the one hand, this approach enables us to visualize newly established research fields and interdisciplinary fields, independent of predefined research categories. On the other hand, co-citation analysis does have several drawbacks. First, the results depend upon how the parameters of the analysis are set, as shown above. In particular, the size of each competency may differ depending on the threshold set for the clustering of publications, resulting in inconsistencies in results across regions and over time. Second, higher citation counts, as observed in the USA and the UK (Figure 2), cannot simply be interpreted as indicating successful development of high-performing research fields because the base levels of citation counts are not fully consistent across scientific disciplines. Furthermore, researcher mobility and funding coordinated among countries are not considered in this study. However, despite these technical limitations, we argue that our results give a reliable indication of the different characteristics of the observed regions and help to explain trends in interdisciplinary spreads.

Stem cell research is an enormously broad scientific field ranging from recent studies on emerging technologies such as iPS cells and miRNAs to standards of medical treatment that were established decades ago. One aim of our study was to illustrate how countries are focusing on different areas; however, there is concern that meaningful strategies might be confused with the arbitrary choices made over multiple decades that have shaped the stem cell fields in these countries. In this regard, greater attention is required to address this issue of diversity by carefully reviewing the background of each competency in depth (i.e., whether the appearance comes from a strategic effort made by the nation, whether it simply reflects a historical strength or research propensities in the nation or whether it is reciprocal).

Conclusion

This study aimed to provide a better understanding of the regional trends and interdisciplinary characteristics of recent scientific research by focusing on the field of stem cells in the USA, China, Japan and the UK. By applying a bibliometric co-citation analysis based on publication footprints, we identified significant differences across countries in terms of regional characteristics, including the number and distribution pattern of competencies, the average growth rate and citation count by country and the composition of scientific disciplines. We examined the validity of research policies and strategies by contrasting these results with other measures, such as patents and clinical trials. We believe that these approaches and findings offer a valuable basis for reviewing research policies and innovation strategies, and hope that this study provides a fresh perspective on regional scientific research that will contribute to a better global outlook.

Future perspective

Stem cell research has been conducted extensively worldwide, and the field has expanded as a result of interdisciplinary collaborations. We find that these characteristics correspond well with downstream factors in the innovation process, particularly with the progress of clinical trials. We speculate that bibliometric approaches enable systematic visualization of the regional characteristics of research, which is expected to provide a substantial fact base that can be leveraged for national scientific and technological policy-making.

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No writing assistance was utilized in the production of this manuscript.

Executive summary

- The bibliometric approach based on co-citation analysis with publication data allows visualization of the volume, quality and interdisciplinary spread of research and development competencies in a specific region.
- The bibliometric approach provides a substantial fact base for technology forecasting and strategic research and development planning and policy-making.
- We identified significant differences across China, Japan, the UK and the USA in terms of regional characteristics, the number and distribution pattern of competencies, the average growth rate and citation count by country and the composition of scientific disciplines.
- Based on these finings, we examined the validity of research policies and strategies by contrasting these results with other measures, such as patents and clinical trials.
- We believe that these approaches and findings offer a valuable basis for reviewing research policies and innovation strategies, and hope that this study provides a fresh perspective on regional scientific research that will contribute to a better global outlook.

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