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Systematic Review

Research Performance in Stem Cell Science and Regenerative Medicine in Iran: A National Comprehensive Observation

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Abstract

Background: Accomplishments in stem cell science and tissue engineering have resulted in a remarkable revolution in the context of future medicine. However, a general insight over the progress of stem cell research in Iran is still lacking. A better understanding of current needs in this field is required to design a better national roadmap.

Methods: In this study, we defined the geographical regions based on the significance of their contribution to stem cell research; then, using the Scopus database, we retrieved reports from Iran and other countries concerning stem cell science and regenerative medicine published from 1994 until the end of 2016.

Results: A significant number of citations belong to North America (6 554 029 citations equal to 49% of the total citations) and Europe (4 425 465 citations equal to 33% of the total citations) and the rest of citations were related to Asia (2 423 352 citations equal to 18% of the total citations). East Asian (2 168 472 citations equal to 76% of the total citations related to Asia) documents were cited more than those from the Middle East (ME) (494 141 citations equal to 17% of the total citations related to Asia) and North and Central Asia (196 382 citations equal to 7% of the total citations related to Asia). Iran as a country in the ME attracted 17% of the total citations related to the Asian countries winning the second position in this regard. The overview of total number of citations showed a sharp increase and upward trend in citation numbers for all the Iranian institutes from 2007 that resulted in the expansion of stem cell science in all major cities of Iran such as Shiraz (8%), Mashhad (5%), Isfahan (5%) and Ahvaz (5%). H-index of Tehran University of Medical Science, which has the highest total citations and document numbers, is the highest among all Iranian research institutes. Citation per paper of Royan Institute (RI) is the highest among the top 10 Iranian institutes, by 13 citations per paper.

Conclusion: Stem cell research in Iran is rapidly developing. Since 2007, the number of published documents in major research institutes increased; thus, there is necessity for analysis of the status of publications in this field and choosing a better direction based on needs. Furthermore, it is necessary to expand and organize international collaborations to enrich our research and benefit from different team experiences.

Keywords: Bibliometrics, Iran, Research Assessment, Regenerative Medicine, Stem Cells, Scientometrics

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Introduction

Accomplishments in stem cell science and tissue engineering have resulted in a remarkable revolution in the context of future medicine. The possibility of generating and genetically modifying stem cells potentially enables us to treat a vast verity of disorders and in particular cases, correct inherited genetic defects.[1-4] Indeed, the study of stem cells as a novel scientific discipline dates back to breakthrough findings reported in the late 1990s (i.e. the cloning of Dolly the sheep)[5] and the first successful derivation of human embryonic stem cells (hESCs) by James Thomson.[6] Since then, stem cell science has gained remarkable attention and public expectation in the potential applications of this science in regenerative medicine raised all over the world.[7] However, this science faced many challenges such as religious and political debates over any manipulation on human embryos for research purposes, somatic cell nuclear transfer technology, ethical and political controversies, and ethical issues regarding cloning human hybrids in different countries.[8-10]

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Despite the limitations and ambiguities, scientists in this field have shown great robustness and ingenuity to attract complementary funding sources for stem cell research, through industries, charities, private sector as well as patient-funded studies.[11,12] North America was the frontrunner in terms of most important metrics of stem cell science, including the number of publications, total citations, patents, clinical trials and funding.[13-15] Many European countries have continuously provided strong support for stem cell research.[16-18] Besides, collaborations within the EU territory has also led to marked achievements in stem cell science.[18,19] Such collaborations developed networks of organizations and individuals that focused on public engagement with stem cells and regenerative medicine in Europe.[18] For instance, a collaboration between scientists and clinicians in Spain, Italy, and the UK led to an innovative experience after the acellularization and re-cellularization of airway tissue replacement in 2009.[20] Although the majority of public health research originated from North America and Western Europe, countries in Asia and Oceania have also benefited from growing support for the development of stem cell research and its applications.[21] Although the progress has not always been smooth, East Asian countries such as China, Korea, Singapore, Taiwan, and India, unprecedentedly have funded stem cell research since 2001. In addition, Japan and Australia, based on their outstanding potential in basic biology and advanced clinical services, established leading stem cell institutes in Kyoto, Kobe, and Melbourne.[22]

Along with other countries, Iran started to invest in ESC research. In the early 2000s, Iran's Supreme Leader, Ayatollah Khamenei, issued a 'stem cell judicial decree' in which it was declared that experimentation with human embryos is consistent with Shia tradition and congratulated the scientists who had produced hESC lines.[23] Hence, Royan Institute (RI) announced the development of the first human ESC line and Iran became the first Muslim country to generate, culture and freeze hESCs in 2004.[24]

Since then, Iran has established several stem cell research centers and the number of active scientists in this field has increased. However, a general insight over the direction of changes and progress across stem cell research is lacking in the country, and a better understanding of the current needs in this field is required. The common research tool for such analyses is the bibliometric methods which have already been widely applied for evaluation of scientific production and research trends in many fields of science.[25] The results of scientometrics analysis could improve the overviews of national research policy-makers regarding the activities of researchers and institutions in this field to make better funding policies. In addition, these findings could help international organizations, such as the World Health Organization, for better understanding the existing potential of Iranian research institutes, which could be considered in regional and/or international projects. Finally, studying the collaborations that have led to highly cited publications could help both Iranian and non-Iranian researchers and/or institutions to identify potential collaborators and enhance collaboration networks.

During recent years, Iran has achieved an outstanding development in medical sciences as well as other fields. A systemic assessment of research performance of academic institutions can be considered a basic prerequisite to manage financial and human resources.[26]

In this study, we aimed to analyze systematically the scientific productivity of Iranian scientists in stem cells and regenerative medicine. We compared and mapped stem cell research in different geographical regions of the country along with the global trends in this field during the period of 1991–2016. The results of this study can help Iranian and non-Iranian scientists to understand the panorama of global stem cell research. The policymakers in this field should also perform further research in this context.

Materials and Methods

Geographic Regions and Countries Included in This Study

The countries within each region were defined as previously described.[21] The six World Health Organization regions are African, Americas, European, South-East Asia, Eastern Mediterranean, and Western Pacific Regions. In this study, we defined the geographical regions based on the significance of their contribution to stem cell research as follows: North America, Europe, and Asia. Asian countries were categorized into three groups namely East Asia, North and Central Asia, and the Middle East. The countries that were merged, separated or changed in any way, between 1994 and 2010, were analyzed considering their current (i.e. 2016) name. Wherever possible, countries with names that have different formats, spelling or abbreviations were identified and all formats of the name were used in the search.

The Search of the Literature

After considering the information obtained through a literature review using scientific databases (Scopus, Google Scholar and Web of Science) and examining the strengths and weaknesses of each database, Scopus was chosen as the information database for this bibliometric analysis because of its enhanced characteristics including vast content coverage, advanced search tools and precise citation analysis. In the present cross-sectional study, we retrieved and downloaded Iranian and non-Iranian studies/reports in stem cell science and regenerative medicine from the Scopus database (http://www.scopus.com) published from 1994 until the end of 2016.

Keywords

"Stem cell" was incorporated in the search string and

qualified these keywords with "keyword tag". We ensured that the main purposes of the study are completely covered by the chosen keywords; so, the following search string was searched in "titles, abstracts, or keywords":

"stem cell" AND "stemness" OR "pluripotency" OR "Regenerative medicine" OR "Tissue regeneration" OR "Tissue engineering" OR "personalized medicine" OR "individualized medicine" OR "cell-based clinical trials" OR "cell-based trials" OR "stem cell therapy" OR "cell therapy" OR "bone marrow transplantation" OR "bone marrow stem cells" OR "iPS cells" OR "induced pluripotent stem cell" OR "ES cells" OR "embryonic stem cell" OR "progenitor cells" OR "Hematopoietic stem cells" OR "hematopoietic cells" OR "Cell differentiation" OR "cellular reprogramming" OR "direct reprogramming" OR "transdifferentiation" AND (EXCLUDE (PUBYEAR , 2017)) AND (EXCLUDE (PUBYEAR , 2018)) AND (EXCLUDE (PUBYEAR , 2019))

The search string was subsequently refined, using analytical functions and tags in Scopus database, by "subject area tags", "country tag", "source title tag", "journal title name" and "affiliation tag", to retrieve data/information on the distribution of publications/scientific output by subject, collaborating countries, author-wise, organization-wise and journal-wise, etc. The selected group were also analyzed by "Analyze search results" of the Scopus website. Then, for each individual document, we retrieved the following information: author name(s), author affiliation(s), subject category(s), journal name(s), publication title(s), and publication year(s), document type and eliminated duplicate records.

For citation data and H-index, citations of publications were collected from the date of publication up to December 2016 and analyzed by Citation overview of the Scopus website while excluding self-citations. The search results were stored in a comma-separated values (CSV) file to include all the essential paper information such as authors' name and affiliations, countries, publication year, citation numbers, journals and H-index.

Analyses and Classifications

In this study, we used common parameters that are considered in scientometrics to evaluate the quality and quantity of publications. All analyses were done in Excel and the graphs were drawn by Keynote software. Based on the analyses and generated data, we tried to draw some conclusions and offer some recommendations.

Results

Overview of Output

The comprehensive search and analysis resulted in retrieval of 4852 documents. Published biodiversity research covered 185 ISI (Information Sciences Institute) identified subject categories in the Science Citation Index (SCI) database. The four most-common categories were medicine (2352 articles equal to 29.0% of the total articles), biochemistry, genetics and molecular biology (2060 articles equal to 25.4% of the total articles), engineering science (570 articles equal to 7.0% of the total articles), materials science (558 articles equal to 6.9% of the total articles) pharmacology, toxicology and pharmaceutics (548 articles equal to 6.8% of the total articles) and finally immunology and microbiology (446 articles equal to 5.5% of the total articles). The most frequent document types were published in peer-reviewed journals are original articles (3950 articles equal to 81.4% of the total articles). Review articles (635; 13.1%), book chapters (95; 2.0%), conference papers (54; 1.1%) and letters (48; 1.0%) were other types of documents. Regarding the publication language, 4577 articles equal to 94.33% of the total articles (4852) were written in English. This observation was consistent with the fact that English was the leading academic language. Besides, most of the SCI-indexed journals were published in English. Other publication languages were Persian (246), Arabic (42), French (2), Portuguese (2), Spanish (1), Turkish (1) and Urdu (1).

The Growth of Stem Cell Research in Iran Contributes to Science Production Worldwide

To find out the contribution of Iranian scientists to global stem cell science, we analyzed total citations of documents in important geographical regions including North America, Europe and Asia (Figure 1a). A significant number of citations belonged to North America (6 554 029 citations equal to 49% of the total citations) and Europe (4 425 465 citations equal to 33% of the total citations) and the rest of citations were related to the Asia (2 423 352 citations equal to 18% of the total citations). The first articles were from North America and Europe are back to 1946 and 1963, respectively; Asia entered the field in 1965. To realize the extent of stem cell research in Asia, we analyzed Asian documents in three important and different geographic regions namely, East Asia, North and Central Asia (NCA) and Middle East (ME), in detail. The analysis revealed that East Asian (2 168 472 citations equal to 76% of the total citations) documents are cited more than articles from ME (494141 citations equal to 17% of the total citations) and NCA (196 382 citations equal to 7% of the total citations). EA and ME were comprised of 15 and 16 countries in this study. In Asia, although the first document was published in the ME in 1965, which was earlier than that published in EA (1967), the EA documents attracted more attention in the field of stem cell. Iran as an ME country attracted 17% of the total citations and was placed in the second position, above Turkey, Saudi Arabia and Egypt (Figure 1, Panel a).

To find out the quality of Iranian publications compared to the other countries, we analyzed citation per paper in the world, Asia and ME (Figure 1b). Furthermore, the quality of publications from different parts of Asia and

different countries was evaluated (Figure 1b).

The comparative timeline representative for the total citation number in the stem cell research and regenerative medicine in different continents and regions showed that Iranian documents' citations increased in 2007 and the upward movement continued until 2016. Indeed, the process is getting close to other leaders of the field, particularly when considering 2014–2016 citations (Figure 1c).

A Strong Collaboration Exists Between Iranian Scientists and Leaders in Stem Cell Research

Evaluation of collaborations between Iran and other countries in this field showed a strong international collaborating network with the United States (395 documents) and United Kingdom (186 documents) as the main associate collaborators. Most of the collaborations were conducted between Tehran University of Medical Science (TUMS), Shahid Beheshti Medical University (SBMU) and RI, and Harvard Medical School and Stanford University School of Medicine in the US and University of Sheffield and University College London (UCL) in the United Kingdom. The majority of Iranian research done in collaboration with the US and UK in stem cell and regenerative medicine was under the subtitle of medicine (48%–50%), followed by engineering and material science (41%–45%) and genetics and molecular biology (43%–47%). The first collaborative articles with the US and UK were published in 2003 and 2002, respectively.

Germany (162 documents) was the second most-collaborating country among European countries. The collaboration of Iranian scientists in this field with Germany started in 2006 and it was more focused on genetics and molecular biology (53%) as well as medicine (43.8%) and engineering and material science (31.5%), in which the Ludwig Maximilian University of Munich and Heinrich Heine University Düsseldorf of Germany were the main collaborating centers with TUMS and RI. Canada (150 documents) and Australia (116 documents) were placed in the fourth and fifth positions and had close scientific collaborations with Iran; particularly, TUMS collaborated with University of Toronto, Canada and University of Queensland, Australia in the field of genetics and molecular biology (47.3– 54.7%). Italy (80 documents), the Netherlands (77 documents) and Sweden

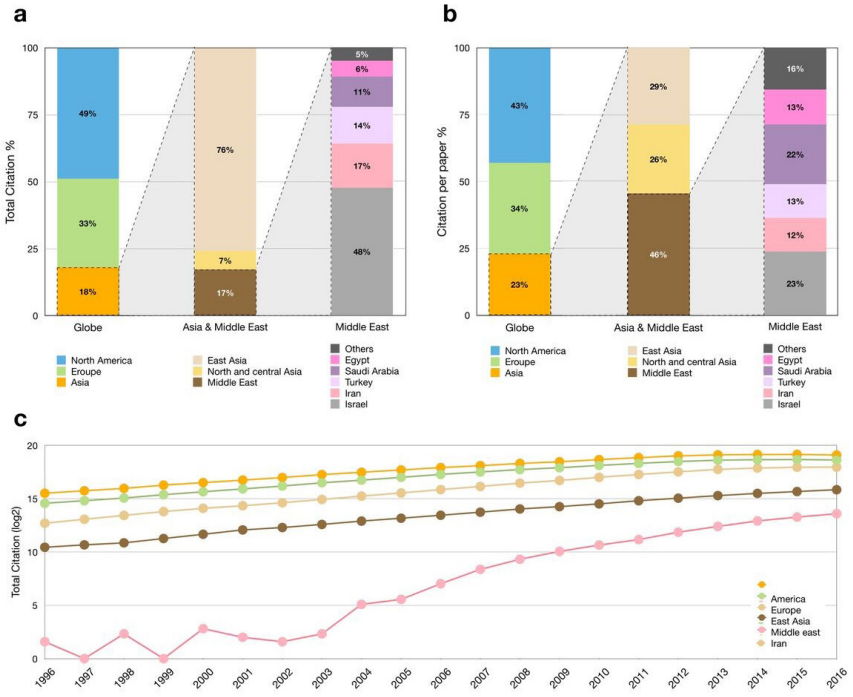

Figure 1. Quantification of Iranian Scientists' Contribution to Stem Cell Research and Regenerative Medicine in Terms of Total Citations and Citation Per Paper Compared to Other Countries. **a)** The geographical distribution of total citations in stem cell research and regenerative medicine in different continents (left column). The contribution of ME scientists to stem cell research and regenerative medicine compared to other Asian scientists (middle column). The right column represents the contribution of different ME countries to stem cell research and regenerative medicine. **b)** The quality of publications in the world considering total citations number from one region per a single paper from the same region (left column). The geographical distribution of citations per paper in the stem cell research and regenerative medicine that represents the quality of contribution in different Asian regions (middle column). The right column represents the citations per paper for different ME countries with regard to stem cell research and regenerative medicine. **c)** The comparative timeline representative for the total citations number in the stem cell research and regenerative medicine in the different continents and regions.
Note: South-East Asia Region: China, Japan, South Korea, Taiwan, Singapore, Hong Kong, Malaysia, Indonesia, Viet Nam, Bangladesh, Macao, Philippines, Mongolia, North Korea, and Myanmar
North and Central Asia Region: India, Russian Federation, Pakistan, Ukraine, Belarus, Kazakhstan, Armenia, Azerbaijan, Uzbekistan, and Kyrgyzstan.
ME: Israel, Iran, Turkey, Saudi Arabia, Egypt, Lebanon, Qatar, the United Arab Emirates, Jordan, Kuwait, Oman, Iraq, Syrian Arab Republic, Bahrain, Palestine, and Yemen.

(71 documents) are European countries that were placed after Canada and Australia. Malaysia (54 documents, University of Malaya) and Japan (38 documents, Osaka University) were the main Asian collaborating countries (Figure 2).

Initiation and Progression of Stem Cell Science in Iran

The timeline of stem cell research (Figure 3a) represents remarkable events and occasions which highlight the progression of the field in Iran. The early 90s, Hematology-Oncology and Stem Cell Transplantation Research Centre was established in Shariati hospital, TUMS, to help patients who are the candidate for bone marrow transplantation and suffer from blood disorders. Afterward, on March 3, 1991, the first hematopoietic stem cell transplantation (HSCT) was performed in this center. From March 1991 through April 2011, a total number of 3237 HSCTs were carried out in this center. This number reached >9000 in 2016 (data unpublished). Then, the center succeeded in execute HSCT and other new methods such as double cord blood, and haploidentical transplantation, as routine clinical care to treat many life-threatening diseases.[27] Seeking for reports on HSCT indexed in Scopus, resulted in retrieval of 446 articles in the field of stem cell research in Iran, which have been cited 4654 times from 1991 to December 2016.

In 1998, James Thomson at the University of Wisconsin-Madison, for the first time, developed a technique to isolate and culture hESCs[6] that was a breakthrough and game changer event in the science that influenced the stem cell research in Iran and other countries. However, isolating the inner cell mass resulted in destruction of the blastocyst, which raised ethical issues, including whether or not embryos at the pre-implantation stage, should be considered to have the same moral or legal status as embryos in the post-implantation stage of development.[28] As already mentioned, after the declaration of 'stem cell judicial decree' in 2002,[23] RI announced the generation of the first hESC line in 2004.[24] Since then, the number of documents published in the field had a significantly increasing trend as shown in Figure 3a (black columns).

Clinical Trials

Along with the progress in the basic embryonic stem cell research, stem cell-based therapies were taken into consideration to benefit patients suffering from a wide range of diseases and injuries. It was expected that the benefits of bone marrow stem cells transplantation in patients who need reconstruction of the hematopoietic and immune systems, would be applied also to other types of stem cell transplants. Hence, good manufacturing practice (GMP) facilities were developed and they led to the production of safe and potent cell-based products to be examined in clinical trials. Therefore, the first clinical trial, using autologous bone marrow-derived stem cell, was

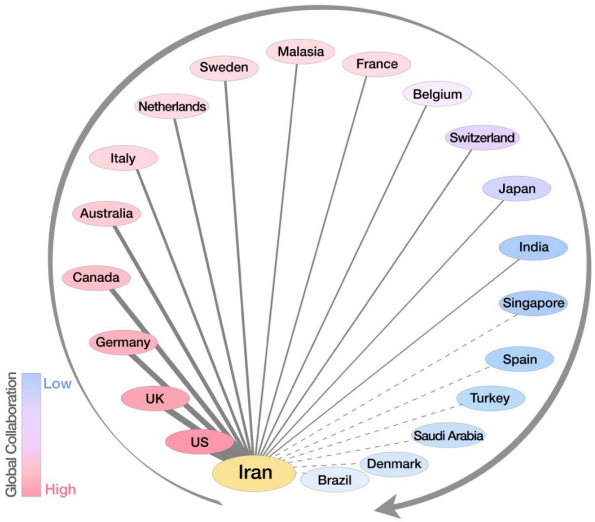

Figure 2. The network of Countries Collaborating with Iranian Scientists in Stem Cell Research and Regenerative Medicine. The weight of dark columns represents the number of mutual publications in stem cell research and regenerative medicine.

conducted in patients with myocardial infarction in 2005, followed by cell therapy trials in skin and liver diseases in the next year. Afterward, cell therapy trials in renal, neurological, and vascular systems, as well as eye and bone diseases, were done by Iranian scientists.[29]

Along with clinical progression, on September 30, 2006, a research group in RI cloned "Royana" in a test tube from an adult cell; "Royana" was registered as the first successfully cloned sheep in Iran and the ME.

In 2006, Shinya Yamanaka launched his groundbreaking discovery, which was a new way to "reprogram" adult, specialized cells to turn them into stem cells. Two years later, Iranian scientists succeeded to produce the first human-induced pluripotent stem cell (iPSCs) that enabled the Iranian scientists to gain better opportunities in research methods for developing, expanding and freezing pluripotent stem cells and generating therapeutic cells from these cells. The reprogramming efforts led to the establishment of the iPSC bank, which includes 106 human-iPSC lines from healthy and diseased individuals.

In 2010, the internationally distinguished "Kazemi Prize", which recognizes valuable international projects in stem cell and regenerative medicine, was introduced. In memory of Dr. Saeid Kazemi Ashtiani (the late founder of Royan Institute), this prize was funded to respect the efforts made in this field. The prize markedly contributed to stem cell sciences development in Iran as it led to information exchange between stem cell leaders and global icons of the field such as Rudolf Yanish, Bob Langer, Hans Schöler and Hans Clevers.

Iranian National Cord Blood Bank, as a public cord blood bank, was established in November 2010. The umbilical cord blood collected samples from 5 hospitals in Tehran.

Royan Stem Cell Technology Co. and Cord Blood Bank were founded in 2005 to take the required steps in the realm of cord blood banking. This center has completed preliminary phases including storing more than 110.000 samples in its public and private banks and opening branches in more than 31 cities of the country. The company established regional branches in almost all neighboring countries.

Iranian Stem Cell Donor Registry is a governmental organization related to Iranian Blood Transfusion Organization that was established in 2009 to help patients who need HSCT. About 70% of patients rely on unrelated volunteer HLA-matched donors.

The Council for Stem Cell Sciences and Technologies (CSCST), affiliated to the Iranian Vice Presidency for science and technology, was established in February 2009 with the aim of accelerating the progress towards stem cell-based treatments.

According to the recent update, there are 94 science-based companies registered in the CSCST.

These companies are doing research in the marketing of products related to stem cell biology and regenerative medicine.

"Sinacell Co." established in 2008 and its mission was industrial development of cell-based products in Iran. This company focused on cell therapy and tissue engineering products in the field of skin, eye and musculoskeletal system. It has marketed two Iranian FDA approved products; Amniosin® and Cell-Amniosin® for treating corneal disorders and diabetic foot ulcer, respectively. Furthermore, several products are in different stages of this company's R&D department.

On February 19, 2013, "Cell Tech. Pharmed Co." was established as an Iranian stem cell and regenerative medicine company, to meet the ongoing demands for stem cell therapy in Iran. "Cell Tech. Pharmed" is a recognized leader in the manufacturing and distribution of cell-based therapies that is currently developing a therapeutic stem cell platform based on discoveries made by RI. The "Barkat Pharmaceutical Group" as a pharmaceutical holding company invested in this project. This company put emphasis on the concept of quality and strict compliance with the rules of current Good Manufacturing Practice (CGMP) in all steps of manufacturing; in Feb 2018, after inspections conducted by Iranian FDA (Food and Drug Administration of Iran), the production site was qualified and the CGMP was certified. The Iranian FDA approved products are: (1) Recolorcell®, autologous melanocyte and keratinocyte for vitiligo, (2) Mesestrocell®, autologous bone marrow mesenchymal stromal cells for osteoarthritis, (3) Renodermcell®, autologous dermal fibroblasts.

Establishment of the first cell-based therapy hospital in Iran was conceived in 2016. RI started negotiations with the Mayor of Tehran at the time, and a place was donated for this purpose. Since then, people are donating money and the site is under construction.

The national document of Stem Cell Sciences and Technologies was also approved as part of the country's national scientific map in September 2013 at the Supreme Council of the Cultural Revolution. Iran's headway towards stem cell sciences and regenerative medicine, despite limited investments, reveals the country's enormous potential to grow in this field.

The "First National Festival and International Congress on Stem Cell and Regenerative Medicine" was held in 2016.

According to the recent report from Iranian FDA, the following companies has registered their products. Some products are approved and the others are under evaluation. (1) Cell Tech Pharmed Co. (2) Sinacell Co. (3) Azmapajouhan Zist Yakhteh Co. (4) Faravardeh Baft Iranian Co. (5) Tissue Regeneration Co. (6) Skin Biotech Borna Co.

Analyzing the total number of publications revealed that the stem cell science is now being practiced in all provinces of Iran. Although at first, the stem cell research was centralized in Tehran, but over time, the science transferred by the trained students to other cities and now there are five stem cell science poles in Iran that produce data on stem cells and numbers of the reports published by these research poles are in the following order: Isfahan (537 documents), Shiraz (511 documents), Tabriz (323 documents) and Mashhad (284 documents). Even small cities such as Bandar Abas (20 documents), Sabzevar (20 documents), Yasouj (19 documents) and Shahroud (17 documents) were recently involved in the field of stem cell science (Figure 3b).

Top Iranian Institutes in Stem Cell Research and Regenerative Medicine

Number of Citations

Top 10 Iranian institutes in the field of stem cell in Iran, based on the number of documents, were perused in detail. Analyzing total citation number and the quantity of publications, H-index, and citations per paper of the selected institutes, revealed progression during the time and demonstrated close competition among these institutes in this field (Figure 4).

The overview of total citations number showed a sharp increase and upward trend in citations number for all the institutes from 2007 (Figure 4a). Professor Ardeshir Ghavamzadeh, a faculty member of TUMS, was the first scientist whose paper was cited in 1996 in this subject for the first time. The most cited documents of TUMS were published in "Advances in Colloid and Interface Science" and "Chemical Society Reviews" in 2011 and 2012, which were cited 552 and 500 times, respectively. TUMS has several referral hospitals and research institutes, as well as the main medical university. Therefore, the majority of TUMS documents are in the field of medicine (59%),

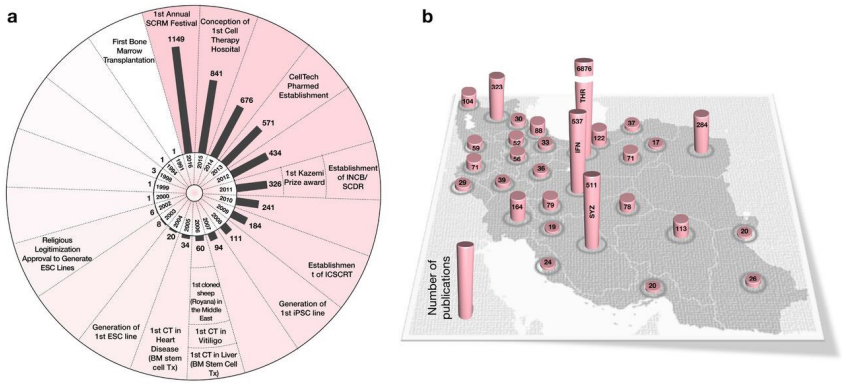

Figure 3. A Comprehensive Graph Representing a Timeline for Research in Stem Cell Science and Regenerative Medicine in Iran and the Distribution of Cities from Where the Documents Were Published. **a)** Representative picture of the number of publications per year since 1991 (black columns) and the breakthrough events in stem cell and regenerative medicine in Iran. **b)** Geographical distribution and comparative analysis of the number of publications in stem cell and regenerative medicine in different provinces of Iran since 1991.

genetics and molecular biology (38%) and immunology and microbiology (11%); however, new progress in the field of engineering and material science (multi-disciplinary research) started in 2003 which is growing so fast and covered 25% of the documents (Supplementary Table 1). The majority of documents of the TUMS is original (82%) and review articles (13%). This institute published most of its documents in "International Journal of Haematology-Oncology" and "Stem Cell Research".

In the next place, RI and Tarbiat Modares University (TMU) stand with almost similar total citations number. Although RI (with 1675 citations) was established later than TMU (with 1628 citations), they shared the second position in terms of total citations number (Figure 4a). The documents of RI were cited for the first time in 2004, but the first citation of TMU dates back to 1996, related to bone marrow stem cells. The most cited documents of RI and TMU were published in "Biomaterial journal" and "Nature protocols" in 2008 and 2009, and they were cited 559 and 344 times up to December 2016, respectively. Hereafter, the most-highly cited Iranian article in the field was from RI (Ghasemi-Mobarake *et al*, 2008, Biomaterials). TMU and RI are both research-based institutes and the majority of their publications are in the field of genetics and molecular biology, 67and 57%, for TMU and RI, respectively. Detailed analysis on the subject of research showed that 44 and 39% of the publications of TMU and RI were categorized in medicine. Both institutes started multi-disciplinary research in collaboration with engineers and biomaterial scientists in 2007, which progressed so fast that 28% of both institutes' documents are classified in this field. The most common type of documents in TMU and RI institutes were original articles, that comprise 86 and 90% of their documents, respectively. The proportion of review articles published by RI (9%) is larger than TMU (7%). Both institutes published most of their documents in the "Cell journal" (Supplementary Table 1).

The SBMU was placed in the third position having 1433 citations number in 2016 and the first citation in stem cell and regenerative medicine in this university dates back to 2000. The document with the highest citations (344 times) published by SBMU is based on a work done in collaboration with TMU (published in 2009 in "Nature protocols"). The medical universities documents are prepared in collaboration with hospitals, hence, most of them are in the field of medicine (55%) and genetic and molecular biology (39%) of stem cells and 28% of the documents are in the field of engineering and materials. SBMU started multi-disciplinary research with engineers and biomaterial scientists in 2008. The majority of the documents in SBMU are original (82%) and review (14%) articles. This institute published most of its documents in "International Journal of Haematology-Oncology" and "Stem Cell Research" (Supplementary Table 1).

Other active research institutes in stem cell science in Tehran, are in the following order (based on the number of publications): University of Tehran (UT, with 866 citations), Islamic Azad University (IAU, with 726 citations), and Iran University of Medical Sciences (IUMS, with 439 citations) (Figure 4a). Among these, IAU is the leader in engineering and biomaterial field as it published 46% of this field's documents while most of the documents published in the field of stem cell and Immunology, belongs to IUMS. The percentage of the original articles of UT (91%) is the highest among other institutes (Supplementary Table 1).

Through the progression of stem cell science in Iran, the institutes of other provinces are also enlisted in the graph while, Shiraz University of Medical Sciences (SUMS, with 724 citations), Tabriz University of Medical Sciences (TBZMED, with 581 citations) and Isfahan University of Medical Sciences (MUI, with 482 citations) were placed in 7 to 9 positions, respectively (Figure 4a). About 67% of the documents of SUMS are in the field of medicine which is the highest rate among other institutes; however, TBZMED mostly focused on pharmacology (34%).

Interestingly, compared to other universities and research centers, the percentage of review articles published by TBZMED is more (26%) in the field of stem cell and regenerative medicine (Supplementary Table 1).

Number of Documents

TUMS was established before any other Iranian institutes and during its 23-years activity in the field of stem cell science and regenerative medicine, it has become the unique pioneer with respect to the publications number (with 1574 documents) (Figure 4b and Supplementary Table 1). The history of research in this subject in TMU dates back to 1994 similar to TUMS; but TMU was placed in the second position with 739 documents. RI was placed in the third position with 640 documents. In other words, TUMS has published 93 documents in each year of its activity. In the fourth position, SBMU, another university in Tehran, published 563 documents up to December 2016. UT is active in the stem cell since 1991, but the total documents of this institute are 362, giving it the sixth position. Research institutes of the other provinces namely, SUMS, MUI and TBZMED are placed in the 7th, 8th and 10th positions with 344, 280 and 238 documents.

Quality of Research

We decided to analyze the ranking of the Iranian institutes by the quality of their publications as well (i.e. by considering "citations per paper and H-index") (Figures 4c and 4d). Citations per paper for RI publications (13 citations per paper) were the highest among the other 10 institutes. TMU and UT are in the next places with 10.58 and 11.06 citations per paper, respectively. TMU and UT institutes were in the second and sixth positions in terms of the total documents and the third and fifth positions regarding total citations (Figure 4, c). However, H-index of TUMS, which is the pioneer in total citations and documents, is still the highest compared to other research institutes (Figure 4d).

The Stem Cell Science in Iran is Generated by Expertise Throughout the Country

The analysis showed that, although the most well-known scientists of stem cell research and regenerative medicine are affiliated in research centers based in Tehran (78%), but in other cities, research in this field is gaining momentum. Therefore, the field is growing by Iranian scientists based in Shiraz (8%), Mashhad (5%), Isfahan (5%) and Ahvaz (5%). The distribution of stem cell scientists in Tehran revealed that the majority of them are working in TUMS (11 out of 30) in which Ardeshir Ghavamzadeh and Kamran Alimoghaddam are the pioneers with 163 and 111 documents, respectively. RI is the second research hub in Tehran with 9 out of 30 of the expertise in the stem cell field. Hossein Baharvand and MH Nasr-Esfahani as the leaders with 266 and 107 documents are affiliated to RI. The other research centers are TMU, Pasteur Institute of Iran (IPI), IUMS and Amirkabir University of technology (AUT) in which Masoud Soleymani (300 documents), MA Shokrgozar (98 documents), E. Seyed Jafari (37 documents) and Ali Samadi Kuchaksaraei (35 documents) are the pioneer scientists of their institutes. AUT is the only engineering-based university that is working in the field of stem cell research in Tehran (Figure 5a).

The pioneer of stem cell research in Shiraz, Mashhad, Isfahan, and Ahvaz are Dr. Ramzi (40 documents), Dr. Bahrami (46 documents), Dr. Ghaedi (43 documents) and Dr. N. Saki (56 documents), respectively (Figure 5, panel a).

Pie charts (Figure 5b) represents the significant (50%) contribution of top 40 scientists (first grade) in total publications on stem cell research and regenerative

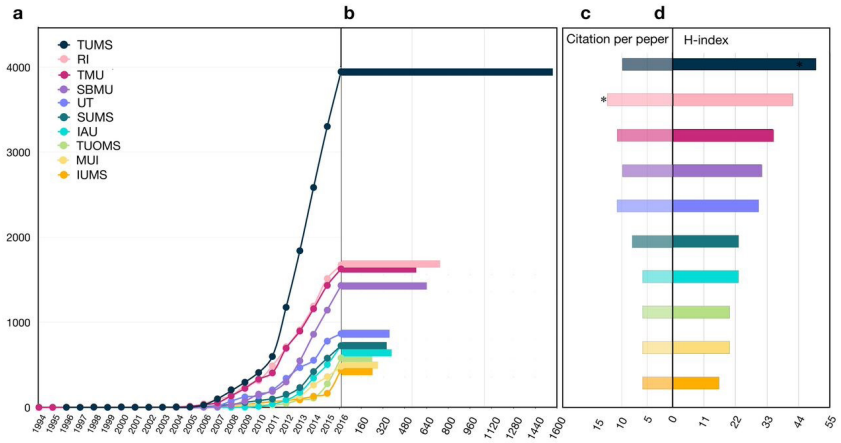

Figure 4. Quantity and Quality of Publications in Stem Cell Research and Regenerative Medicine in Iran According to the Scientometrics Parameters in Top Stem Cell Research Centers of Iran. **a)** The trend of total citations per year; b) Total publications number for the top 10 research centers in the stem cell research and regenerative medicine in Iran since 1994. **c)** The schematic graphical representation of citations per paper; **d)** The H-index of top 10 research centers in stem cell research and regenerative medicine in Iran since 1994. An asterisk marks the top institute in each topic.

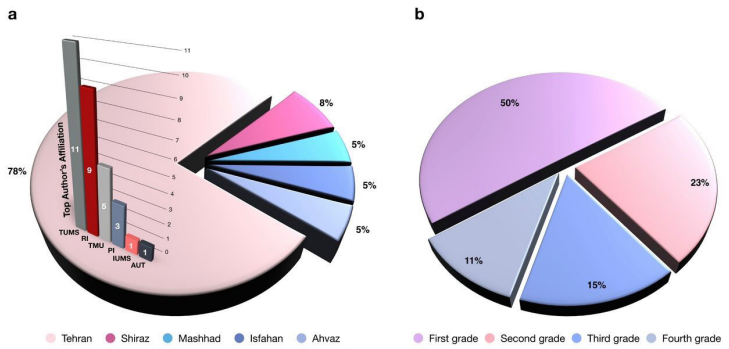

Figure 5. Geographical Distribution of Top 40 Iranian Scientists Sorted Based on the Number of Documents Published from Different Provinces of Iran and Their Contribution to Stem Cell Research and Regenerative Medicine.

medicine in Iran. According to the number of total publication, first-grade scientists (those with ≥32 documents) generated 50% of total documents. Second grade (those with 23–31 documents) and third grade (those with 19–22 documents) generated 23 and 15% of total relevant documents in Iran, respectively. The fourth grade (those with ≤18 documents) contributed to 11% of total publication in stem cell research and regenerative medicine (Figure 5b).

Conclusion

In conclusion, stem cell research in Iran is rapidly growing and developing. Although since 2007 the quantity of generated documents in major research institutes increased, we need to analyze the current status and choose better direction based on what we need. Furthermore, we need to increase and organize international collaborations to enrich our research. As a take home message, we would like to recommend two important points to bibliometric specialists in universities and research centers. (1) Please check the affiliation address of all authors and inform them about registered affiliation addresses. This will help you to have better performance compared to other universities and research centers. (2) Using "MeSH terms" will help your publications to be seen and cited more.

Authors' Contribution

SS: literature review and analysis; RK: analysis and graphs; PM, MK, BEB, ZH: data collection, data analysis; HB, FA, MV: concept, design of study, writing manuscript, proof reading.

Conflict of Interest Disclosures

Authors hereby declare there is no conflict of interest.

Ethical Statement

This original article registered and approved at ethics committee, Royan institute, Tehran, Iran. IR.ACECR.ROYAN.IREC.1398.51.

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Supplementary Materials

Supplementary file 1 contains Table S1.

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