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Executive Report

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Contents

Summary 1

Background 2

Materials and methods 3

Results 5

Discussion and conclusion 7

Tables 8

Figures 12

Summary

This report is a bibliometric analysis of the growth rates of publications in the fields of stem cells and tissue engineering and regenerative medicine in Iran and compares these rates with the rates in other regions of the world. PubMed database was used for extraction of relevant publications using MeSH terms. The data were extracted from 2001-2011 and the address fields of the publications were checked manually in order to allocate the publications to a relevant geographical region. Linear regression was used for fitting a linear model to the publications of a particular region and the slope of the model was used as an indicator of publication growth rate. Statistical comparison of the slopes of different regions showed that Iran enjoys a moderate growth rate in regards to tissue engineering and regenerative medicine publications (including stem cells-related papers) and a low growth rate in regards to general stem cells papers. Iran is a regionally dominant country in the field of tissue engineering but, not in the field of stem cells. Analysis of the annual growth rate showed a steady pattern of growth of tissue engineering papers and a random pattern of growth for general stem cells papers. This is an indication of instability in the general stem cell research and stability in the field of tissue engineering. Due to equal research funding opportunities, this observation is explained by the natural selection of the latter field by Iranian biomedical scientists. This natural selection should be supported and followed by policy makers in order to take advantage of current research interests and capabilities. It is recommended to view and manage stem cells research as a part of regenerative medicine not *vice versa*.

Background

The fundamental concepts of enhancement of natural regeneration process in human tissues and application of integrated engineering and biological technologies to produce tissue substitutes have been the focus of many in-depth experimental and clinical studies for more than two decades. The principal elements that have been used for materializing these concepts are cells, biomaterials and soluble factors. The advances in cell biology and engineering have made the majority of scientists to believe that stem cells are the most viable cell sources to be included in the above triad. Therefore, tissue engineering and regenerative medicine have been strongly linked to the stem cell biology and *vice versa*. As the result, the science policy makers regulate stem cells and tissue engineering research, practice and funding under the same policy or two very closely interacting policies.

Policy making would not be accurate without having a proper account of current, past and estimated future research and professional activities. As, still tissue engineering and stem cells are predominantly in the research phase and their integration into many promised clinical management protocols is pending, measurement of the status of these fields is better achieved by assessment of the “research” activities. Bibliometric analysis has been long used as one of the useful method for evaluation of activities and output of a particular research field, and has been used for preparation of this report.

Several online databases are available for extraction of biomedical bibliometric data including, but not limited to, PubMed, Web of Knowledge, Scopus and Google Scholar. None of these databases include all the published works and each of them has its own search engine and capabilities. The data from each of these databases could be

extracted using the database-specified keywords or the operator-specified keywords. Database-specified keywords usually give more consistent results, which will yield more accurate conclusions in comparative bibliometric studies. Database-specified keywords exist for stem cells, tissue engineering and regenerative medicine in PubMed under its MeSH terms, which makes it a very useful source for extraction of data in these fields. However, other sources do not include accurately organized database-specified keywords for these fields, which necessitate the use of operator-specified keywords.

The usefulness of operator-specified keywords in accurate identification of published works depends on the field of study. For the “stem cells” literature, there is a high possibility that the terms “stem cell” or “stem cells” are mentioned in the title, abstract or keywords of a publication. Therefore, “stem cells” or “stem cell” could be used as keywords for extraction of stem cells-related publications with high precision from most databases. However, the field of tissue engineering and regenerative medicine is so heterogeneous that operator-generated keywords will not be able to accurately identify the relevant publications, which will highly affect the accuracy of subsequent comparative analyses. As the result, this report used PubMed database and its MeSH terms for extraction of publications data.

This report studies the growth rate of publications in the fields of stem cells and tissue engineering and regenerative medicine in Iran and compares it with the growth rate in other regions of the world.

Materials and methods

PubMed has been used for extraction of published articles in the fields of tissue engineering and regenerative medicine and stem cells. The search has been conducted

using MeSH terms (table 1). The search strategy for retrieval of tissue engineering and regenerative medicine publications included:

> "Tissue engineering"[MESH] OR "Regenerative Medicine"[MESH] OR Regeneration[MESH] OR "Guided Tissue Regeneration"[Mesh] OR "Cell engineering"[MESH] OR "Tissue Scaffolds"[MESH] OR "Biocompatible Materials"[MESH] OR "Cell Transplantation"[MESH] OR "Bioartificial Organs"[MESH]

For retrieval of stem cells publications, the following search strategy has been used:

> "Stem cells"[MESH]

The data were retrieved on 15th January 2013 and the address fields of the retrieved publications were checked manually in order to allocate each publication to the following geographic locations according to the World Bank's classification of countries:

> Europe, North America, South America, Africa, Australia, East Asia, South Asia, Middle East, Iran

The publications with no address were excluded from the study. As, at the time of information retrieval, the indexing of 2012 publications by PubMed was not complete, the 2012 publications were not included in this study. The data were retrieved from 1965 (the date of introduction of the first regenerative medicine-related MeSH term) up to 2011. Central Asian countries had only a hand count of publications in these fields and so, were excluded from this study. The distribution pattern of the extracted publications identified the 14 Iranian publications before the year 2001 as outliers, and so, the publications before the year 2001 were excluded from the study.

GraphPad Prism 5.01 (August 7, 2007, GraphPad Software, Inc, www.graphpad.com) has been used for analysis of data. The general rate of the growth of publications output in the above geographical regions was calculated by linear regression analysis and calculation of the slope of the best fit line. The resulting slopes in geographic regions were compared using Prism's ANCOVA-based comparison and a p value of less than 0.05 was considered statistically significant.

In addition to the above general growth rate, an annual growth rate (AGR) was calculated for each region and field using the following formula:

$$Annual\ Growth\ Rate\,(\%) = \frac{Current\ Year\ Total - \Pr evious\ Year\ Total}{\Pr evious\ Year\ Total} \times 100$$

Results

A total of 166'216 publications were included in this study of which 118'733 were tissue engineering and regenerative medicine papers, and 62'500 were stem cells papers of which 15'017 were on the subject of tissue engineering and regenerative medicine. Tables 2-4 show the temporal and regional distribution of these publications.

Linear regression was used for determining the best fit linear model to describe the general growth rate in each region. As the slope of the model in each region is a true representative of the growth rate, the slopes were compared by an ANCOVA-based method and showed the highest growth rate in East Asia, Europe and North America, moderate growth rate in South America, South Asia, Australia, and Middle East and the lowest growth rate in Africa. The growth rate of Iran lied within the group with the moderate rate of growth (table 5). The rates of growth of scientifically dominant

countries in each region were not significantly different from the regional rates (data not shown). Therefore, Iran could be considered as one of the Middle Eastern dominant countries in the field of tissue engineering and regenerative medicine. Figure 1 shows the growth models of these regions in comparison with Iran. Acceleration of the growth rate in Africa after 2007 makes its rate statistically insignificant in comparison with the rate of growth of Iran from 2007-2011.

The percentages of annual growth rates (AGRs) of tissue engineering and regenerative medicine are shown in figure 2. The highest growth rate in Iran is observed in 2004 and steadily decreases afterward. However, it is consistently higher than the average AGR in Middle East, Europe, North America and Australia.

For the stem cells publications, the regions could be classified into four groups according to their growth rates (table 6). North America, East Asia and Europe show the highest growth rate and their rate in this field is higher than their growth rate in regenerative medicine. Iran is classified as a country with low growth rate and its rate of growth is significantly lower than the general rate in the Middle East. Therefore, Iran is not considered as a dominant Middle Eastern country in the field of stem cells research. An interesting finding is that in technologically advanced North American, East Asian and European countries the growth rate in stem cells research output is far higher than tissue engineering. This difference is not observed in other regions (tables 5 and 6). The regression models of the growth trends in stem cells publications are presented in figure 3.

Figure 4 presents the AGRs of stem cells publications in different regions. Iran has shown a high peak of 600% in 2006, which could be due to the negative rate in 2005.

The rates of growth in Iran and in Africa are inconsistent showing some instances of random negative and high growth rates.

Analysis of stem cells publications related to the field of tissue engineering and regenerative medicine showed some interesting findings (table 7). In this category, the countries could be classified into two groups of high and moderate growth and Iran is included in the group with moderate growth. The growth rate of Iran is the same as the rate of Middle East and so, Iran is considered as a dominant country in the region for this category. The growth models in this area are presented in figure 5. The inconsistency in the Iranian annual growth rate is observed in the same way that was described for the general stem cells publications.

Discussion and conclusion

This study reports that the publication output of Iranian biomedical scientists in the field of tissue engineering and regenerative medicine shows a growth rate consistent with the general growth rate in the Middle East and other countries with moderate growth rate. However, the same pattern is not observed in regards to the stem cell research publications. The basic stem cell research is following a low rate of growth in Iran. The findings of the current study show that Iran is a dominant country in the field of tissue engineering in the region but this is not true about the general stem cell research. This dichotomous observation could be a reflection of the interest of Iranian biomedical scientists to applied research, which arises from the immediate needs of biomedical community.

As a general rule, the needs determine the field of research and highly affect its sustainability. Annual growth rate (AGR) is one of the well established indicators for assessment of sustainability. AGR for the Iranian tissue engineering publications

shows an organized steady pattern of growth. However, AGR for Iranian general stem cells publications shows an unpredicted and random pattern of growth, which is a reflection of instability of research in this field.

In Iran, stability and regional dominance in the field of regenerative medicine research, which receives the same degree of support as stem cells, is an indication of natural selection of this field by biomedical scientists and its prioritization over that of general stem cells research. This natural selection should be supported and followed by policy makers in order to take advantage of current research interests and capabilities. The finding that, in the last decade, the growth rate of Iranian tissue engineering publications did not show any statistically significant difference with a developed country like Australia is an emphasis to the importance of natural selection. Therefore, it is recommended to view and manage stem cells research as a part of regenerative medicine not *vice versa*.

A combined bibliometric and questionnaire-based study is recommended to complement this brief assessment and determine the Iranian biomedical community's needs for policy interventions.

Table 1. MeSH terms used for retrieval of information from PubMed

MeSH term	Date of introduction
Regeneration (first introduced as bone regeneration)	1965
Biocompatible Materials	1972
Stem cells	1984
Cell Transplantation	1994
Bioartificial Organs	2001
Tissue engineering	2002
Regenerative Medicine	2004
Guided Tissue Regeneration	2005
Tissue Scaffolds	2008
Cell engineering	2012

Table 2. Distribution of tissue engineering and regenerative medicine publications

Date	Europe	North America	South America	Australia	Africa	East Asia	Central Asia	South Asia	Middle East	Iran
2001	2254	2709	101	152	31	1027	1	70	142	4
2002	2693	3051	125	145	31	1292	0	73	129	4
2003	2896	3424	151	155	32	1628	0	105	161	7
2004	3087	3645	148	208	40	2008	1	116	223	15
2005	3461	3954	154	219	56	2186	1	128	199	19
2006	3598	4151	223	253	39	2299		137	236	35
2007	3658	4039	257	289	55	2546	1	167	278	58
2008	3998	4407	302	269	77	2685	0	169	289	76
2009	4166	4606	342	301	79	3001	1	244	349	93
2010	4450	4866	412	337	97	3182	0	235	362	106
2011	4585	4830	377	365	105	3322	0	321	418	129
Total	38846	43682	2592	2693	642	25176	5	1765	2786	546

Table 3. Distribution of stem cells publications

Date	Europe	North America	South America	Australia	Africa	East Asia	Central Asia	South Asia	Middle East	Iran
2001	808	1232	18	58	5	379	1	5	41	0
2002	917	1556	21	70	1	465	0	7	45	0
2003	1061	1597	28	88	0	614	0	19	56	2
2004	1119	1896	35	94	5	795	0	14	78	4
2005	1340	2040	40	105	4	1017	0	31	67	2
2006	1579	2368	50	133	6	1213	0	34	131	14
2007	1789	2534	48	147	4	1441	0	38	118	28
2008	2124	3017	67	143	5	1794	1	44	134	24
2009	2253	3040	77	185	18	1789	0	85	149	35
2010	2573	3339	114	210	10	2198	1	85	170	46
2011	2720	3486	118	202	22	2389	1	95	207	75
Total	18283	26105	616	1435	80	14094	4	457	1196	230

Table 4. Distribution of stem cells publications in the field of tissue engineering and regenerative medicine

Date	Europe	North America	South America	Australia	Africa	East Asia	Central Asia	South Asia	Middle East	Iran
2001	110	207	2	12	2	56	0	2	10	0
2002	181	334	3	7	0	98	0	3	11	0
2003	235	373	5	17	0	136	0	5	14	0
2004	256	457	4	20	0	201	0	4	27	0
2005	332	499	7	22	3	274	0	7	22	0
2006	406	600	6	40	1	318	0	6	39	0
2007	428	607	8	36	1	387	0	8	32	11
2008	492	722	9	35	1	455	0	9	35	5
2009	552	714	24	42	5	469	0	24	48	12
2010	640	825	24	38	3	602	0	24	46	12
2011	648	815	22	46	8	617	0	22	57	23
Total	4280	6153	114	315	24	3613	0	114	341	63

Table 5. The slopes of the linear models of tissue engineering and regenerative medicine publication growth in each geographic area

Group	Region	Slope ± SE	Intergroup P Value*	Between groups P Value*
Highest growth rate	East Asia	171.4 ± 32.51	P > 0.05	P < 0.05
	Europe	155.6 ± 39.48		
	North America	136.3 ± 43.72		
Moderate growth rate	South America	24.69 ± 4.741	P > 0.05	
	Middle East	21.77 ± 3.990		
	South Asia	18.99 ± 2.805		
	Australia	16.62 ± 3.560		
	Iran	11.90 ± 1.211		
Low growth rate	Africa	5.955 ± 1.266		

* Prism's ANCOVA-based analysis for comparison of slopes in linear regression model

Table 6. The slopes of the linear models of stem cells publication growth in each geographic area

Group	Region	Slope ± SE	Intergroup P Value*	Between groups P Value*
Highest growth rate	North America	231.5 ± 8.492	P > 0.05	P < 0.05
	East Asia	208.4 ± 8.457		
	Europe	202.0 ± 9.591		
Moderate growth rate	Middle East	16.11 ± 1.357	P > 0.05	
	Australia	15.55 ± 0.9687		
Low growth rate	South Asia	9.336 ± 1.019	P > 0.05	
	South America	9.918 ± 1.101		
	Iran	6.582 ± 0.9907		
Very low growth rate	Africa	1.591 ± 0.4401		

* Prism's ANCOVA-based analysis for comparison of slopes in linear regression model

Table 7. The slopes of the linear models of growth of stem cells publication related to tissue engineering and regenerative medicine in each geographic area

Group	Region	Slope ± SE	Intergroup P Value*	Between groups P Value*
High growth rate	East Asia	60.70 ± 9.701	P > 0.05	P < 0.05
	Europe	58.80 ± 6.737		
	North America	51.90 ± 12.31		
Moderate growth rate	Middle East	6.100 ± 1.170	P > 0.05	
	South America	4.300 ± 1.656		
	South Asia	4.290 ± 1.546		
	Australia	2.300 ± 1.005		
	Iran	3.100 ± 1.561		
	Africa	1.600 ± 0.5657		

* Prism's ANCOVA-based analysis for comparison of slopes in linear regression model

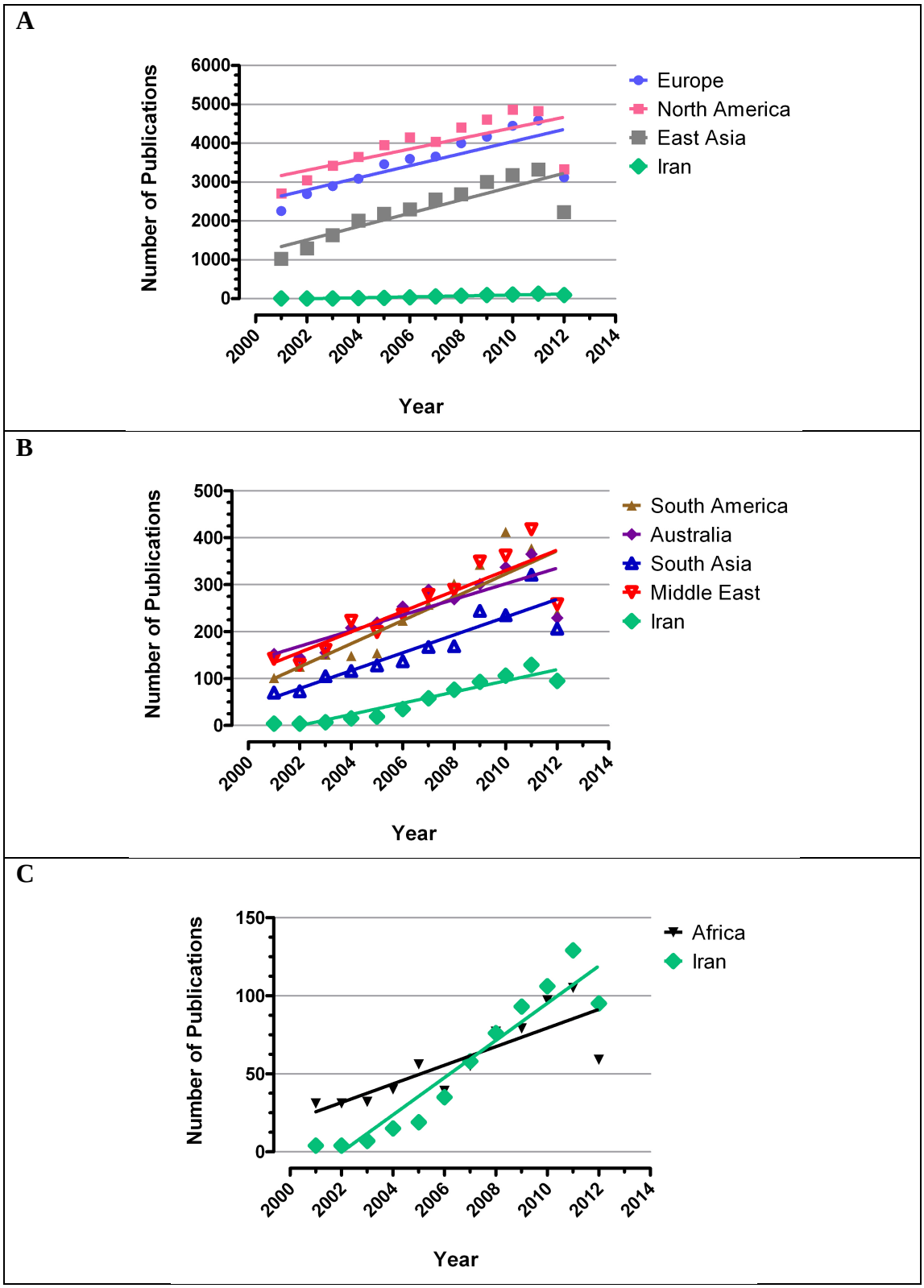

Figure 1. The linear models of tissue engineering and regenerative medicine publications growth in Iran and other world regions

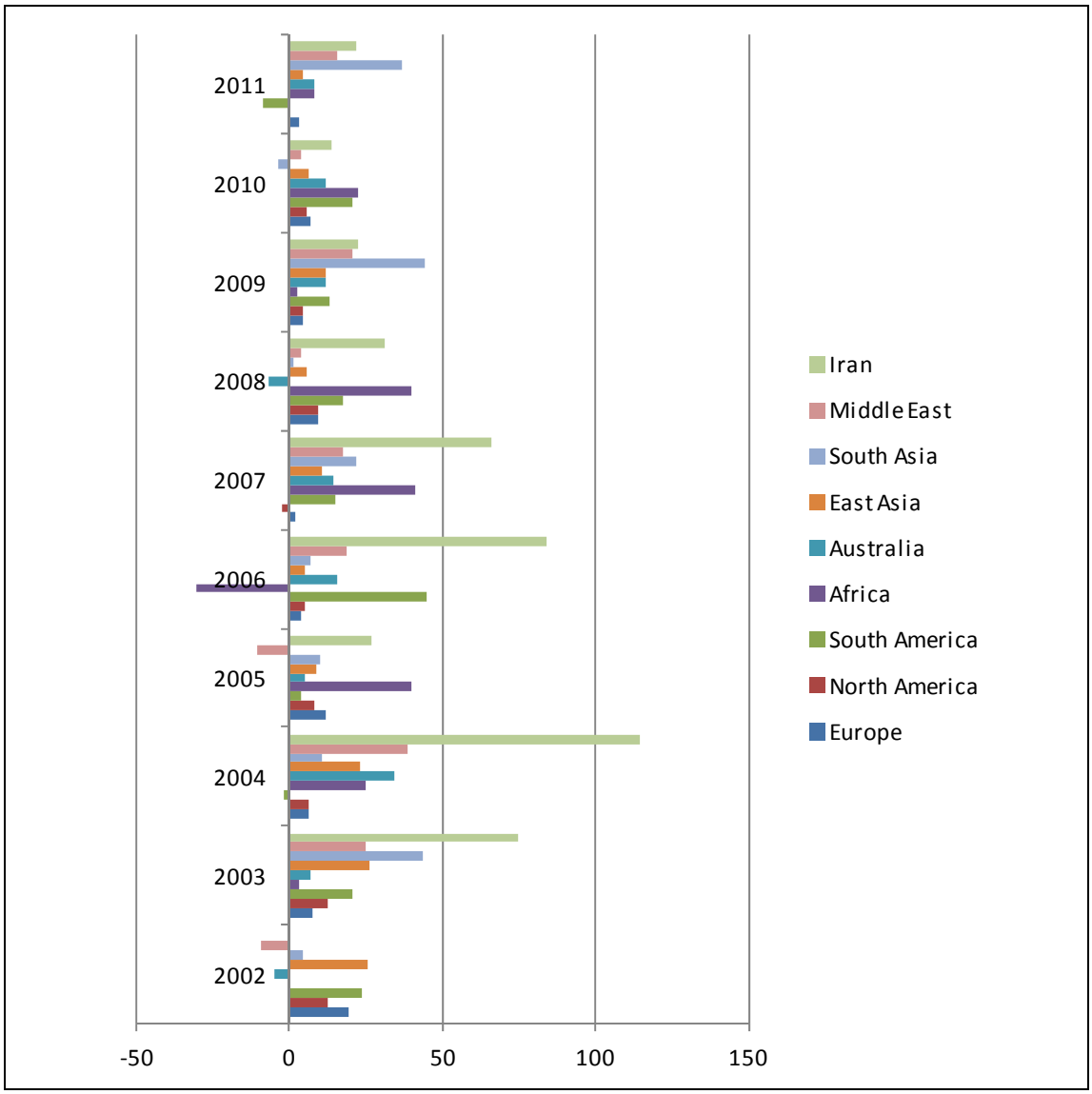

Figure 2. The annual growth rates of tissue engineering and regenerative medicine publications in Iran and other world regions

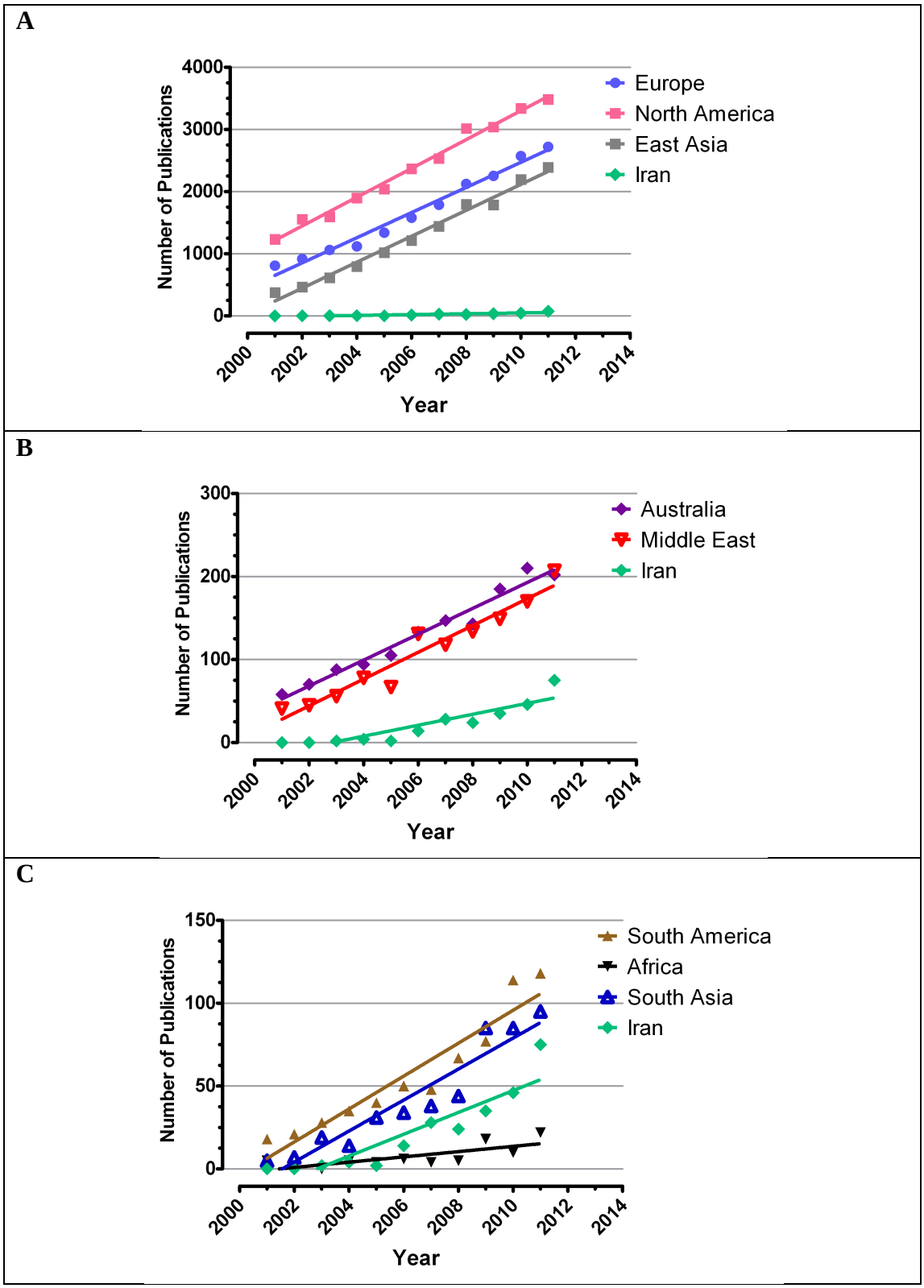

Figure 3. The linear models of stem cells publications growth in Iran and other world regions

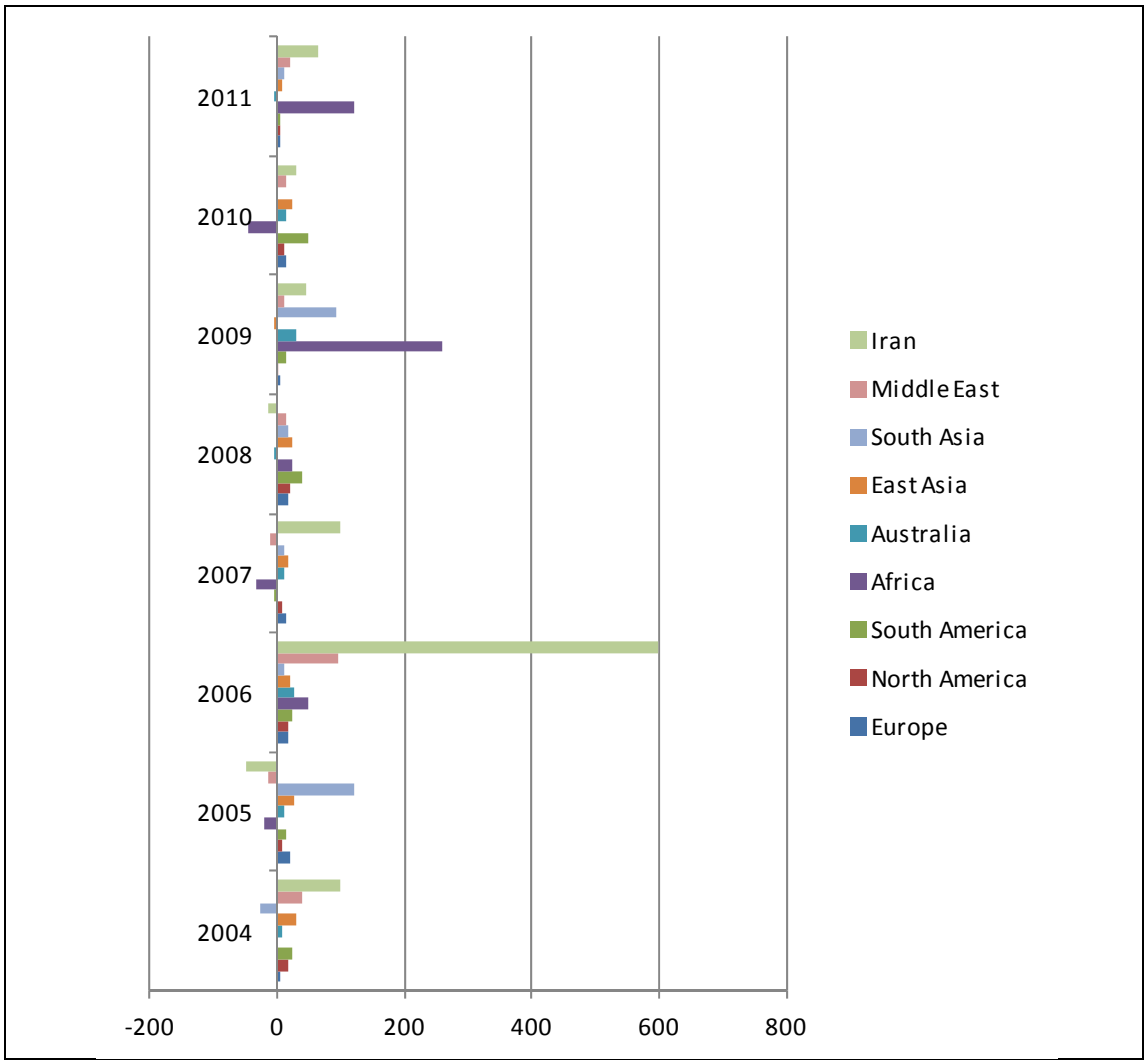

Figure 4. The annual growth rates of stem cells publications in Iran and other world regions

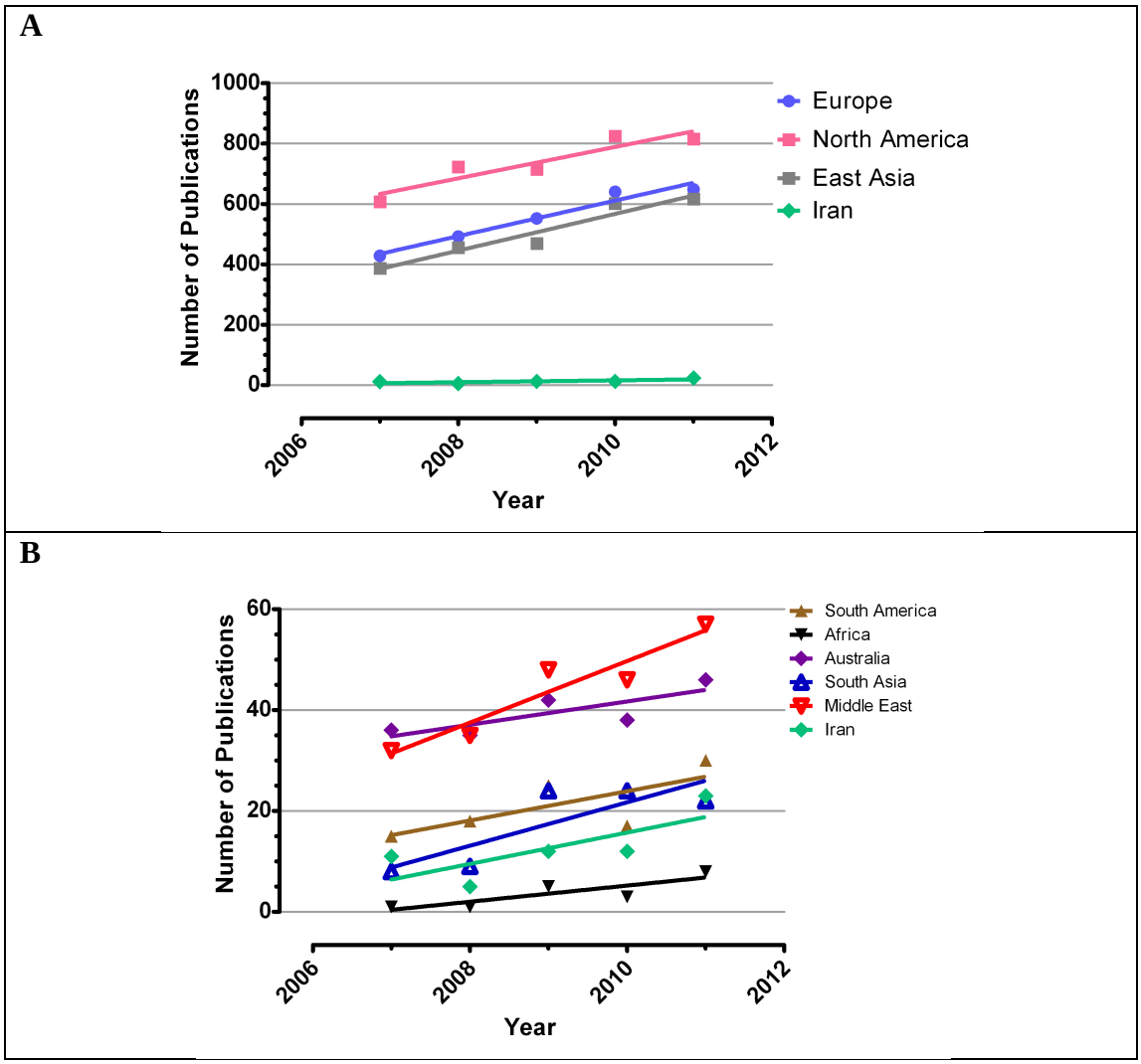

Figure 5. The linear models of growth of stem cells publications related to tissue engineering and regenerative medicine in Iran and other world regions

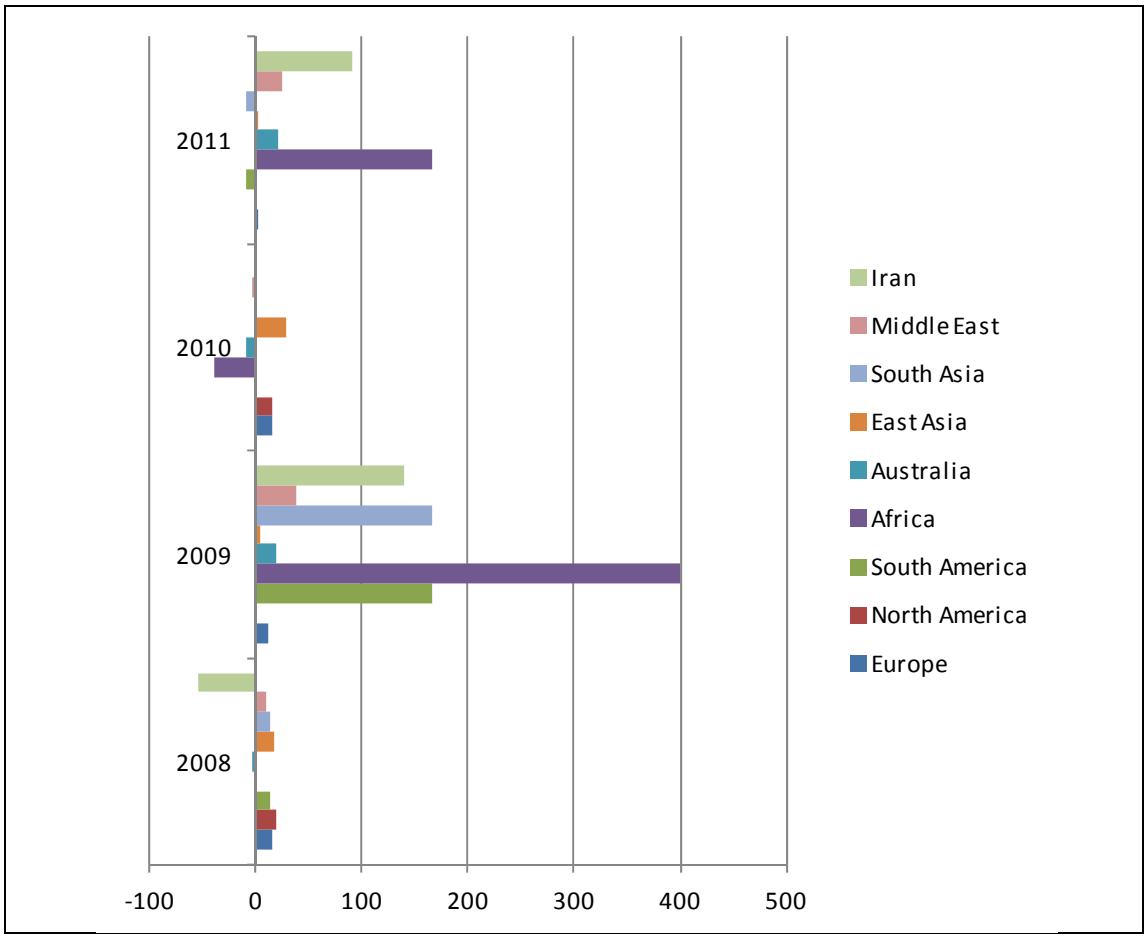

Figure 6. The annual growth rates of stem cells publications related to tissue engineering and regenerative medicine in Iran and other world regions

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