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Global tissue engineering trends. A scientometric and evolutive study.

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Abstract
Tissue engineering is defined as a multidisciplinary scientific discipline with the main objective to develop artificial bioengineered living tissues in order to regenerate damaged or lost tissues. Since its appearance in 1988, tissue engineering has globally spreaded in order to improve current therapeutical approaches, entailing a revolution in clinical practice.
The aim of this study is to analyze global research trends on tissue engineering publications in order to realize the scenario of tissue engineering research from 1991 to 2016 by using document retrieval from Web of Science database and bibliometric analysis. Document type, language, source title, authorship, countries and filiation centers and citation count were evaluated in 31,859 documents.
Obtained results suggest a great multidisciplinary role of tissue engineering due to a wide spectrum —up to 51— of scientific research areas identified in the corpus of literature, being predominant technological disciplines as Material Sciences or Engineering, followed by biological and biomedical areas, as Cell Biology, Biotechnology or Biochemistry. Distribution of authorship, journals and countries revealed a clear imbalance in which a minority is responsible of a majority of documents. Such imbalance is notorious in authorship, where a 0.3% of authors are involved in the half of the whole production.

Keywords
Tissue engineering — Global trends — Evolution — Bibliometric analysis

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Contents

Introduction

Tissue engineering (TE) is one of the most relevant areas in Advanced Therapies research that has been developing for more than 30 years. TE applications are focused on the development of biological substitutes that can restore, maintain or even improve the structure or functionality of damaged tissues [1, 2]. Tissue engineering, as it is recognized today, was introduced by Y. C. Fung in 1988 when he submitted a proposal to the National Science Foundation (NSF) for an Engineering Research Center to be entitled "Center for the Engineering of Living Tissues" [3]. Since then, it has been described in literature a widespread of TE applications for regeneration of bone [4], cartilage [5], skin or blood vessels [6] among others. These bioengineered tissues and organs play a key role in therapeutics as they are considered as medicines [7]. In this sense, research on TE leading to biomimetic regeneration techniques constitute one of new major approaches for future therapeutical applications.

Due to the accumulation of scientific information, an attempt of gathering systematic metadata about the global production in TE-related research can be used for the identification of hotspots and main topics within the field of knowledge. In this milieu, bibliometric methodology is a tool that provides quantitative analysis from publications. Bibliometric analysis aims to identify the corpus of literature within a given subject area, as TE, by content or citation analysis [8,9]. Studying the origin, format, type and citation count of published journal articles provides an insight into the quantity and scholarly impact of reported research. Evaluation and understanding of the international trends in research output provides valuable insight into the direction of TE in the future. Even more, bibliometrics provides relevant information in translational research and advanced therapies as it identifies the most developed issues that are close to clinical translation and, thus, experimental promotion and funding is worthy. In this sense, bibliometrics have been already performed for analysis of global trends in many medical disciplines [10–16]. However, bibliometric analysis has not been applied for the study of the literature corpus in TE, except for Dai, Yang and Li who analyzed 314 documents from 1987 to 1999 [17].

Digitalization of scientific information and the availability of new tools for metrics (statistics, bibliographic software, page ranks, social media. . .) allow the analysis of the impact and distribution in a large variety of ways [8]. In this sense, sometimes the huge account of available documents about a consolidated subject or the wide heterogeneity of the thematic field makes hard and difficult an analysis of all data. Thus, representative sampling is performed by selecting documents of a specific geographic region [18–20], an specific thematic journal [21–23] or top-cited documents of the subject area [24–27]. TE is considered an emerging research field and it would be interesting to analyze all reported documents to visualize global trends and distribution, as it has been reported in other emerging areas [28–30].

The aim of this study is to analyze global research trends on tissue engineering publications in order to realize the scenario of global tissue engineering research from the beginning to nowadays and, therefore, the impact, the characteristics and spread of TE in medicine. Data extracted from this analysis could play a key role to determine the most productive areas in the evolution of TE in order to promote a clinical translation and, therefore, a better approach to solve relevant human diseases and injuries.

1. Methods

The metadata used in this study were obtained from the Web of Science (WoS) core collection database of the Institute for Scientific Information (ISI) (Philadelphia, PA, USA). WoS is considered one of the most complete and reliable databases of scientific information, as it gathers information of 8,917 scientific journals. Citation data provided by ISI is one of the main advantages of WoS besides other scientific databases as MedLine.

Documents were retrieved by searching (“TISSUE ENGINEER*” or “TISSUE-ENGINEER*”) as topic on SCI-Expanded collection, within a period range between 1991 and 2016. Obtained results were analyzed by publication type. Then, further bibliometric analysis was performed on articles by excluding reviews, book chapters, meeting abstracts and proceeding papers. Once obtained, all the journal articles referring to TE in the past 26 years (from 1991 to 2016) were assessed by the following criteria: languages, WoS research areas and categories, source title, countries, filiation institutions, authors and citation count. Leading to a further comprehension of global trends, some of these analyses were performed over 3 time groups: (1) from 1991 to 1999, (2) from 2000 to 2008 and (3) from 2009 to 2016. The selection of these ranges were adjusted to global production taking into account that the amount of documents is higher as time goes nearer to nowadays.

2. Results

2.1 Document type and language

A total of 41,588 documents were retrieved from ISI Web of Science after performing the search strategy described previously, corresponding to 26 years of global production that form the corpus of literature at TE. As it can be shown in Figure 1, journal article is the dominant type of document as it appears up to 31,859 documents (76.61 % of the corpus), followed by 5,004 reviews (12.03% of the corpus), 2,859 meeting abstracts (6.87%) and 1866 proceeding papers (4.48%).

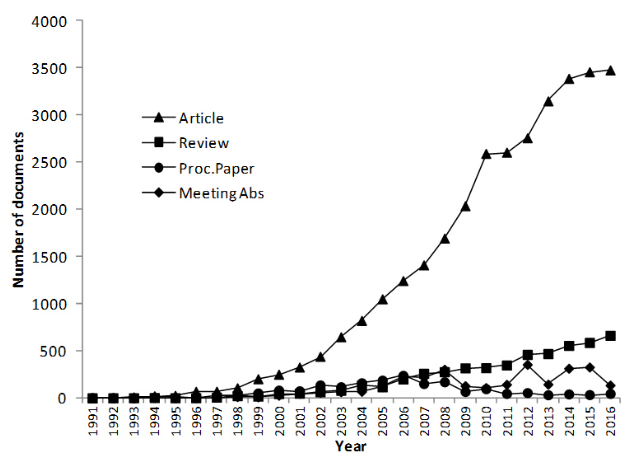

Figure 1. Publication of documents referred to TE assessed by type of document from 1991 to 2016. Evolution shows a remarked increasing trend being journal article the dominant type of document followed by review, proceeding paper and meeting abstract.

Publication of journal articles has been increasing from the beginning and especially during last years. Review production shows similar increasing trend. Other documents type are less remarkable as meeting abstract that maintained annual amount of publication during last decade Proceeding papers also show a slight decreasing trend from 2008 to nowadays.

Cumulative journal article production by year, as seen in Figure 2, adjusts to exponential and potential model with $R^2 = 0.945$ and 0.9643 respectively. Furthermore, third-degree polynomic model showed to be the most accurate model ($R^2 > 0.999$) for predictions on future production. Using the polynomic function $y = 2.743x^3 – 24.195x^2 + 19.946x + 144.1$, it can be predicted that literature will double by 2023. Besides, near 2027 the amount of article journals related to TE will be three-fold current number.

Regarding the language of publication, the vast majority of journal articles are written in English (98.05%), while there are less than 2% of documents which uses other language as German (0.60%), Chinese (0.52%), Korean (0.43%), French (0.11%), Japanese (0.08%) or Spanish (0.05%). These results show the relevance of English as the language that most of research areas use for global communication of new findings.

2.2 Research areas

Distribution of the corpus of literature in research areas resulted more heterogeneous as recent years were assessed (data not shown). At the beginning of the series, in 1991, all documents were distributed among 5 research areas. In 2016, published articles could be found among 151 research areas, which emphasize the growth of the discipline as well as its interdisciplinary role.

In Figure 3A it is shown the growth rate of journal articles grouped by subject areas WoS declared subject areas. It can be appreciated an steady increase of production, mainly in the most productive categories such as ”Material Science”, ”Engineering”, ”Cell Biology” and ”Biotechnology & Applied Microbiology”. Furthermore, WoS subject categories can be clustered in 3 thematic areas (Technology, Physical sciences and Life Sciences & Biomedicine) and obtained results showed that almost all studied years, scientific article production derives from Technology area (Figure 3B). When all the documents in the corpus are assessed, 55.10% of documents are located in Technology area, followed by 27.26% documents in Life Sciences & Biomedicine and 17.64% derived from Physical Sciences. Contribution of physical sciences to TE shows an increasing trend, especially from 2000 to 2016 while Life Sciences & Biomedicine input is slightly increasing. Role of Technology research areas remains constant and higher than 50% during last decade. When the total count of cites was analyzed (Figure 3C), the distribution pattern among thematic areas was very similar to document analysis with Technology as the dominant area of knowledge.

2.3 Source title

A total of 2070 journals have reported at least one of the 31,859 scientific articles. However, up to 1380 journals (66.67%) have published less than 5 documents, being considered as minority sources and, thus, disposable. These results are in accordance with Bradford’s law of scattering which postulates that most of documents reported in an specific area located in a minority of sources. Table 1 presents the 20 most productive journals (source titles are abbreviated) globally and by time ranges. Bold-typed in table 1 represents core journals at each range as determined by Bradford nuclei that cluster 25% of all documents. A total of 8 journals compose the core journals in TE, being Biomaterials, Journal of Biomedical Materials Research Part A and Tissue Engineering Part A the source of 15% of the corpus.

Results attending to 2009-2016 range are very similar to global results because of the exponential increase of scientific production that gathers 73.48% of articles in the last 7 years. 1991-1999 and 2000-2008 series show more reduced Bradford nuclei with only 3 core journals reporting 25% of documents. Biomaterials, as the most productive journal in all time series, reported more percentage of documents at the earlier stages of TE development, from 10.79% documents in 1991-1999, to 5.75% documents in 2009-2016. Similar results were obtained for Journal of Biomedical Materials Research whose production decreased from 10.02% in 1991-1999 to 5.33% in 2009-2016 (adding parts A and B). These results may not only imply the raise of documents per year, but also the emergence of a huge number of new journals, mainly during recent years.

2.4 Country distribution

An assessment of countries where manuscripts were generated revealed USA as the most important country in term of TE scientific production participating in 8782 documents (27.75%). Next origin country in production is China with 4836 documents (15.28%), followed by Germany (5.95 %), Japan (5.77%) and South Korea (5.13%). It is remarkable the increase trend of TE in Asiatic countries as China, producing from 0.19% of documents in 1991-1999 to 17.84% in 2009-2016; and South Korea, from 1.93% in 1991-1999 to 5.47% in 2009-2016. Table 2 summarizes a list of the 20 countries with the higher amount of journal articles and percentages. Global diversity is not only evident after studying source title but also country distribution as the number of countries with more than 10 documents was 4 (14.81%) in 1991-1999; 32 (60.38%) in 2000-2008 and 53 (63.86%) in 2009-2016 (data not shown).

2.5 Institutions and research centers

Harvard University (3.00%), University of California System (2.60) and Massachusetts Institute of Technology (1.81%), all of them sited in USA, appeared as the institutions generating the greater number of articles based on TE. Together with Chinese Academy of Sciences (1.78%) and University of London (1.72%) constitute the top five centers on TE research and produce more than 10% of global production. During the early stage of TE (1991-1999) there was a majority of American institutions that established the foundation of TE, in coexistence with some German and Japanese universities. From 2000 to nowadays, it can be observed a quick arise of Asiatic institutions as the Chinese Academy of Sciences, Shanghai Jiao Tong University or the National University of Singapore, being these among the 10 most productive institutions and mainly responsible of the development of TE as a

1991-1999			2000-2008			2009-2016			TOTAL		
J	C	%	J	C	%	J	C	%	J	C	%
Biomaterials	56	10,79	**Biomaterials**	1010	12,83	**Biomaterials**	1338	5,75	**Biomaterials**	2404	7,6
J Biomed Mater Res	52	10,02	**Tissue Eng**	597	7,58	**Tissue Eng Part A**	1015	4,36	**J Biomed Mater Res Part A**	1475	4,66
Biotechnol Bioeng	31	5,97	**J Biomed Mater Res Part A**	500	6,35	**J Biomed Mater Res Part A**	975	4,19	**Tissue Engin Part A**	1103	3,48
Tissue Eng	26	5,01	Biomacromolecules	176	2,23	**Acta Biomaterialia**	947	4,07	**Acta Biomaterialia**	1035	3,27
J Biomater Sci Polym Ed	19	3,66	J Biomed Mater Res Part B	137	1,74	**Mater Sci Eng C Mater Biol Appl**	523	2,25	**Tissue Eng**	623	1,97
Cell Transplant	13	2,5	J Mater Sci Mater Med	122	1,55	**J Tissue Eng Regen Med**	459	1,97	**Mater Sci Eng C Mater Biol Appl**	523	1,65
Clin Plast Surg	13	2,5	J Biomed Mater Res	121	1,54	**Tissue Eng Part C Methods**	425	1,83	**J Tissue Eng Regen Med**	514	1,62
J Mater Sci Mater Med	12	2,31	Biotechnol Bioeng	118	1,5	**J Mater Sci Mater Med**	367	1,58	**J Mater Sci Mater Med**	501	1,58
Ann Biomed Eng	11	2,12	J Biomater Sci Polym Ed	114	1,45	Plos One	350	1,5	Biomacromolecules	489	1,54
Proc Natl Acad Sci USA	10	1,93	Ann Biomed Eng	103	1,31	Biomacromolecules	313	1,35	Tissue Eng Part C Methods	444	1,4
Gen Eng News	8	1,54	Acta Biomaterialia	88	1,12	RSC Adv	302	1,3	J Biomed Mater Res Part B	403	1,27
MRS Bulletin	8	1,54	Tissue Eng Part A	88	1,12	ACS Appl Mater Interfaces	267	1,15	J Biomater Sci Polym Ed	385	1,22
Macromolecules	8	1,54	J Orthop Res	85	1,08	J Biomed Mater Res Part B	266	1,14	Plos One	360	1,14
Biotechnol Prog	7	1,35	Artif Organs	80	1,02	J Mater Chem B Mater Biol Med	263	1,13	Ann Biomed Eng	323	1,02
J Cell Biochem	7	1,35	Biochem Biophys Res Commun	68	0,86	J Biomater Sci Polym Ed	252	1,08	Biotechnol Bioeng	312	0,99
J Orthop Res	6	1,16	J Biomech	57	0,72	Biomed Mater	230	0,99	RSC Adv	302	0,95
Cytotechnology	6	1,16	Int J Artif Organs	56	0,71	Ann Biomed Eng	209	0,9	ACS Appl Mater Interfaces	267	0,84
Nat Biotechnol	6	1,16	Macromol Biosci	55	0,7	Colloids Surf B Biointerfaces	209	0,9	Biomed Mater	266	0,84
Laryngorhinootologie	6	1,16	J Tissue Eng Regen Med	55	0,7	Carbohydr Polym	201	0,86	J Mater Chem B Mater Biol Med	263	0,83
In Vitro Cell Dev Biol Anim	6	1,16	Osteoarthritis Cartilage	53	0,67	J Appl Polym Sci	180	0,77	Macromol Biosci	231	0,73

Table 1. Analysis of documents referred to TE by source title from 1991 to 2016. Bradford nuclei that cluster 25% of all documents are represented in bold type, showing Biomaterials, Journal of Biomedical Materials Research Part A and Tissue Engineering Part A as the three most productive journals. J: Journal name; C: Document count; %: Percentage of documents.

research area A summary of the more relevant filiation centers producing TE articles is shown in Table 3.

2.6 Authorship of documents

67,231 researchers have been detected as authors in any TE scientific article. Nonetheless, the vast majority of these participations are singular as there are 41,081 authors with a single participation. Even more, 0.3% of authors are involved in 50% of TE articles, which is a clear example Lotka's law of scientific productivity in which the number of authors and the number of contributions closely follows the function $y = 87120/x^{2.4}$ ($R^2 = 0.981$), meaning an inversely proportional exponential relation between authors and contributions. In fact, 20 first most productive authors, detailed in Table 4, have participated of up to 10% of total articles from 1991 to 2016. Rui L. Reis, Dave L. Kaplan and Antonios G. Mikos are the most relevant authors when taking into account the whole corpus. During the first stages of TE development, Robert Langer was the most remarkable researcher with 8.09% authorship of all the publications during 1991-1999. From 2000 and beyond, TE exponentially increase and Antonios G. Mikos (1.13% of documents between 2000 and 2008) and Rui L. Reis (1.07% of documents between 2009 and 2016) appeared as the most productive researchers.

2.7 Citation analysis

Total citation count was obtained from WoS as an index of the global impact of TE articles. In this sense the average citation of all articles resulted in 27.26 citing articles per document, and the Hirsch-index was up to 266. Due to the huge amount of articles reported last years (73.48% of documents have been published during last 7 years), there are yet 35.00% of documents with less than 5 cites. With respect to the most relevant reports, 5.39% documents accumulate more than 100 cites, 0.24% of total documents achieved more than 500 cites. Finally, the corpus of keystone papers, considered as articles with more than 1000 cites, is formed by 16 documents. The most relevant article for TE gathers 5631 cites (LangerVacanti 1993), which means that 17.24% as maximum of TE articles have cited it (assuming that only TE articles have cited it). A selection of the 10 top-cited TE articles is detailed in Table 5.

3. Discussion

TE appeared for first time in 1988 as an alternative clinical approach when transplantation of living tissues has failed or would fail [3]. Few years later, Langer and Vacanti defined TE as a new scientific discipline with the main objective of develop artificial bioengineered living tissues in order to regenerate damaged or lost tissues [2]. Nowadays, this original goal has become a revolution in clinical practice and for the first time the treatment of some diseases and injuries is based on TE applications included in what it is known as advanced therapies. In this sense, oral mucosa, skin, bone, cartilage or blood vessels [31] are examples of artificial tissues generated by TE.

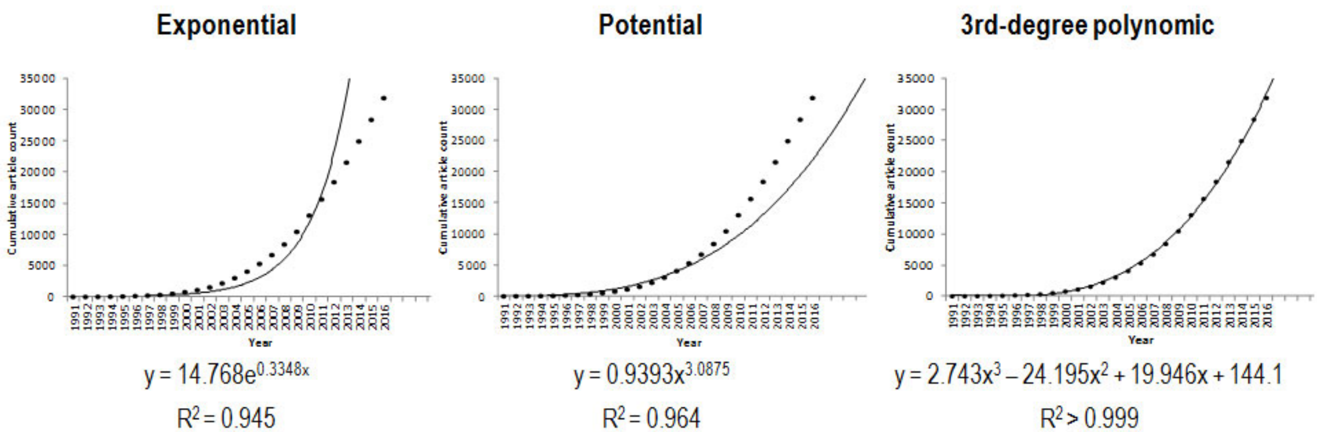

Figure 2. Cumulative journal article production by year. Analysis adjust to exponential, potential and polynomic model respectively shows the most accurate correlation coefficient for polynomic equation ($R^2 > 0.999$)

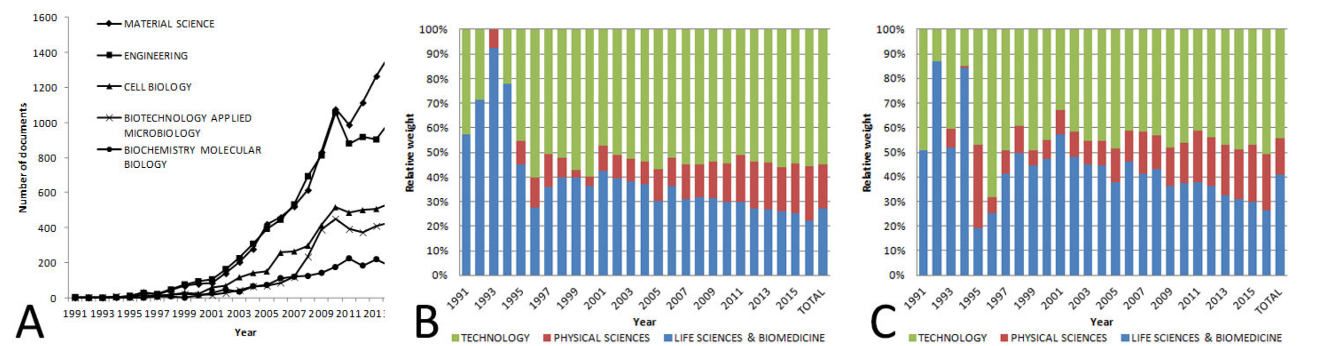

Figure 3. Growth rate of documents grouped by WoS declared subject areas from 1991 to 2016. Material Science, Engineering and Cell Biology represent the most productive areas (A). Relative weight of documents (B) and cites received by TE documents (C) distributed by WoS categories of knowledge.

In response to this clinical promising approach, TE as a research area has globally spread leading to a significant increase in scientific production. To perform this study we analyzed the corpus of literature and not only a sample based on a journal, a region or a period of time. A limitation of our study is that an important fraction of literature could be ignored taking into account that terms like "regenerative medicine", "tissue engineering" or "cell therapy" are sometimes used interchangeably [32]. However, it is acceptable, especially for regenerative medicine and tissue engineering, not to consider them as synonymous, with the former emphasizing the cellular regenerative aspect of tissue replacement and the latter emphasizing the engineering and manufacturing aspect of tissue replacement [33] . In this article, we have especially selected the terms "tissue engineer*" OR "tissue-engineer*" to perform our research trying to emphasize this last aspect as previously indicated. Our interest was to retrieve all the production that researchers themselves considered as tissue engineering. An early report about global TE trends was carried out between 1987 and 1999 analyzing 314 available documents [17]. Nowadays, the huge increase of TE scientific production and digitalization of information during the last two decades make possible not only the evaluation of a relevant number of documents but also to consider how TE has evolved through the years. In this sense, bibliometric methods could contribute to the identification of active focuses of research over time and also to the definition of the growth pattern and the historical framework of the discipline. Moreover, bibliometric data have been widely employed to compare the research output of different institutions [34], design of public funding [35] and collaborations [36].

In our study, a total of 41,588 documents were retrieved from ISI Web of Science after performing the search strategy described previously, corresponding to 26 years of global production that form the corpus of literature at TE. Although the distribution of publications by basic research, translational research and clinical application appears to be an important to understand the structure of TE corpus of literature [37], the aim of this study was to assess the global scenario where TE research occur rather than to evaluate the status of an specific research (basic, translational or clinical) for each document.

Several methods have been used to differentiate among the types of research carried out in the documents [37, 38]. Both the procedure suggested by Narin associating journals with type of research [38] and the procedure postulated by Lewison and Paraje using keyword analysis [37] are in discussion and new reliable methods are needed at this purpose [39].

As it can be shown in Figure 1, journal article is the dominant type of document as it appears up to 31,859 documents (76.61% of the corpus), followed by 5,004 reviews (12.03% of the corpus), 2,859 meeting abstracts (6.87%) and 1,866 proceeding papers (4.48%).

In this sense, cumulative journal article production by year, as seen in Figure 2, adjusts to exponential and potential model with $R^2 = 0.945$ and 0.9643 respectively. Furthermore, third-degree polynomic model showed to be the most accurate model ($R^2 > 0.999$) for predictions on future production. Using the polynomic function $y = 2.743x^3–24.195x^2 + 19.946x + 144.1$ it can be predicted that literature will double by 2023. The publication of TE articles in journals through the time showed an increase in number as has been previously described in other disciplines [13, 15, 40]. This pattern of growth can be adjusted to an exponential model with a correlation coefficient near to 95%, as Price' exponential law postulates [41]. Besides, near 2027 the amount of article journals related to TE will be three-fold current number.

However during last years (from 2011 to nowadays) the number of documents did not reach the values than could be expected following this model. A better adjustment is achieved when we use a third degree polynomic model with a correlation coefficient higher than 99.9%. Following this polynomic model it can be predicted that the total amount of TE articles obtaining from the origin of the discipline to nowadays will be doubled just in the next seven years. By far, global production will be three fold current number in 2027.

This pattern of growth resembles a Gompertz function which is a sigmoideal model used to predict the development of a discipline [42]. According to this in the evolution of a subject it can be described three stages. Firstly, an early stage composed by the precursors and the seminal articles followed by a second stage in which the growth of articles closely adjust to an exponential pattern constituting the forefront of research. Finally, during the last stage the publication rate slowly decrease becoming lineal and the main objective is not the maintenance of the forefront of research but the archive of obtained knowledge and consolidation of the discipline.

Our results suggest that the evolution of TE might be on a transition between the forefront and consolidation stages as it has followed an exponential model until 2011. From 2011 to the present the growth rate is under the exponential model. This finding, together with the fact that the main document type in recent years, apart from journal articles, was the review also suggests that TE is not an emerging area but a consolidating discipline.

1991-1999			**2000-2008**			**2009-2016**			**TOTAL**		
	C	**%**		**C**	**%**		**C**	**%**		**C**	**%**
USA	281	54,14	USA	2804	35,61	USA	5697	24,49	USA	8782	27,75
Germany	42	8,09	China	685	8,7	China	4150	17,84	China	4836	15,28
Japan	40	7,71	Japan	664	8,43	South Korea	1272	5,47	Germany	1884	5,95
Canada	21	4,05	Germany	611	7,76	Germany	1231	5,29	Japan	1825	5,77
Italy	10	1,93	England	514	6,53	Japan	1121	4,82	South Korea	1623	5,13
Korea	10	1,93	Korea	341	4,33	England	891	3,83	England	1414	4,47
Switzerland	10	1,93	Italy	278	3,53	Italy	835	3,59	Italy	1123	3,55
England	9	1,73	Netherlands	232	2,95	India	724	3,11	Canada	893	2,82
Netherlands	6	1,16	Canada	224	2,84	Canada	648	2,79	India	772	2,44
Australia	5	0,96	Switzerland	187	2,37	Iran	577	2,48	Netherlands	708	2,24
France	4	0,77	Singapore	160	2,03	Australia	474	2,04	Taiwan	619	1,96
Turkey	4	0,77	Taiwan	146	1,85	Netherlands	470	2,02	Iran	598	1,89
Scotland	3	0,58	France	144	1,83	Taiwan	470	2,02	France	582	1,84
Taiwan	3	0,58	Spain	80	1,02	France	434	1,87	Australia	553	1,75
Belgium	2	0,39	Australia	74	0,94	Spain	415	1,78	Singapore	550	1,74
Finland	2	0,39	Austria	67	0,85	Singapore	390	1,68	Switzerland	512	1,62
Austria	1	0,19	Israel	59	0,75	Portugal	348	1,5	Spain	495	1,56
Czech Republic	1	0,19	Sweden	57	0,72	Switzerland	315	1,35	Portugal	393	1,24
China	1	0,19	Belgium	52	0,66	Brazil	237	1,02	Brazil	265	0,84
Denmark	1	0,19	Turkey	50	0,63	Turkey	204	0,88	Turkey	258	0,82

Table 2. Analysis of documents referred to TE by country from 1991 to 2016. The research reveals USA, China and Germany as the most important countries in term of TE scientific production during the period studied. C: Document count; %: Percentage of documents.

1991-1999			2000-2008			2009-2016			TOTAL		
	C	%		C	%		C	%		C	%
Massachussets Institute of Technology	63	12.14	Harvard University	340	4.32	University of California System	575	2.47	Harvard University	952	3.00
Harvard University	55	10.60	University of California System	229	2.91	Harvard University	557	2.39	University of California System	823	2.60
University of Michigan	29	5.59	Massachussets Institute of Technology	213	2.71	Chinese Academy of Sciences	457	1.96	Massachusetts Institute of Technology	573	1.81
Rice University	24	4.62	Rice University	181	2.30	Shanghai Jiao Tong University	445	1.91	Chinese Academy of Sciences	563	1.78
University of California System	19	3.66	University of Michigan	181	2.30	Sichuan University	376	1.61	University of London	544	1.72
VA Boston Healthcare System	19	3.66	PennsylvaniaCommonwealth System of Higher Education	168	2.13	University of London	374	1.60	Shanghai Jiao Tong University	506	1.60
Massachusetts General Hospital	17	3.28	University of London	164	2.08	National University of Singapore	337	1.45	Pennsylvania Commonwealth System of Higher Education	504	1.59
Humbolt University of Berlin	14	2.70	National University of Singapore	155	1.97	Universidade do Minho	330	1.42	University of Michigan	502	1.58
Kyoto University	14	2.70	VA Boston Healthcare System	151	1.92	Pennsylvania Commonwealth System of Higher Education	324	1.39	National University of Singapore	492	1.55
Northwestern University	13	2.51	University System of Georgia	149	1.89	Massachussets Institute of Technology	297	1.27	Sichuan University	438	1.38
Free University of Berlin	12	2.31	Imperial College London	133	1.69	University of Michigan	292	1.25	University System of Georgia	409	1.29
Pennsylvania Commonwealth System of Higher Education	12	2.31	Georgia Institute of Technology	131	1.66	Centre Nationale de la Reserche Scientifique	280	1.20	Rice University	403	1.27
University of Munich	12	2.31	University of Pennsylvania	129	1.64	University College London	263	1.13	Universidade do Minho	380	1.20
University of Pittsburgh	12	2.31	University of Pittsburgh	126	1.60	Indian Institute of Technology	250	1.07	University College London	374	1.18
University System of Georgia	12	2.31	Massachusetts General Hospital	118	1.50	Tsinghua University	249	1.07	Centre Nationale de la Recherche Scientifique	367	1.16
Charite Medical University of Berlin	11	2.12	University of Toronto	110	1.40	University System of Georgia	248	1.06	University of Pittsburgh	366	1.15
Georgia Institute of Technology	11	2.12	Chinese Academy of Sciences	106	1.35	Institut National de la Sante et de la Recherche Medicale	230	0.99	Tsinghua University	344	1.09
University of Minnesota System	11	2.12	University College London	105	1.33	University of Pittsburgh	228	0.98	Georgia Institute of Technology	342	1.08
Johns Hopkins University	10	1.93	University of Science Technology	96	1.22	Seoul National University	224	0.96	University of Toronto	323	1.02
Laval University	10	1.93	Tsinghua University	94	1.19	Nanyang Technological University	217	0.93	VA Boston Healthcare System	318	1.00

Table 3. Analysis of documents referred to TE by institution from 1991 to 2016. During this period Harvard University, University of California System and Massachusetts Institute of Technology were the most important centers in terms of TE production. C: Document count; %: Percentage of documents.

Publication of journal articles has also been increasing from the beginning and especially during last years. Review production shows similar increasing trend. Other documents type are less remarkable as meeting abstract that maintained annual amount of publication during last decade. Proceeding papers also show a slight decreasing trend from 2008 to nowadays.

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Bibliometric methods have also been used for providing information about the contribution of diverse disciplines to global production in a scientific area [8]. These methods would allow us not only the assessment of global trends and evolutive patterns but also the discovery of up-and-coming fields [9] which is key for the promotion of translational research and development.

Originally, TE was defined as an interdisciplinary field that applies the principles of engineering and the life sciences towards the development of biological substitutes in order to restore, maintain or even improve tissue function [2]. In fact, either Technology, Physical Sciences or Life Sciences and Biomedicine categories, which are the three scientific branches used by WoS, have contributed to TE evolution revealing the multidisciplinary role previously mentioned.

Distribution of the corpus of literature in research areas resulted more heterogeneous as recent years were assessed (data not shown). At the beginning of the series, in 1991, all documents were distributed among 5 research areas. In 2016, published articles could be found among 151 research areas, which emphasize the growth of the discipline as well as its interdisciplinary role. Moreover, Figure 3 shows the growth rate of journal articles and the citation counts of the publications grouped by subject areas WoS declared subject areas. It can be appreciated an steady increase of production, mainly in the most productive categories such as “Material Science”, “Engineering”, “Cell Biology” and “Biotechnology & Applied Microbiology”.

Furthermore, WoS subject categories can be clustered in 3 thematic areas (Technology, Physical sciences and Life Sciences & Biomedicine) and obtained results showed that almost all studied years, scientific article production derives from Technology area. When all the documents in the corpus are assessed, 55.10% of documents are located in Technology area, followed by 27.26% documents in Life Sciences & Biomedicine and 17.64% derived from Physical Sciences. Contribution of physical sciences to TE shows an increasing trend, especially from 2000 to 2016 while Life Sciences & Biomedicine input is slightly decreasing. Role of Technology research areas remains constant and higher than 50% during last decade. It is important to point out that scaffold and extra-

1991-1999			2000-2008			2009-2016			TOTAL		
A	C	%	A	C	%	A	C	%	A	C	%
Langer, R.	42	8.09	Mikos, A. G.	89	1.13	Reis, R. L.	248	1.07	Reis, R. L.	295	0.93
Vacanti, J. P.	23	4.43	Langer, R.	77	0.98	Kaplan, D. L.	157	0.68	Kaplan, D. L.	208	0.66
Mikos, A. G.	22	4.24	Vacanti, J. P.	66	0.84	Liu, Y.	154	0.66	Mikos, A. G.	196	0.62
Freed, L. E.	18	3.47	Athanasiou, K. A.	57	0.72	Mano, J. F.	144	0.62	Boccaccini, A. R.	184	0.58
Mooney, D. J.	18	3.47	Boccaccini, A. R.	55	0.70	Zhang, Y.	139	0.60	Liu, Y.	180	0.57
Sittinger, M.	16	3.08	Vunjak-Novakovic, G.	55	0.70	Boccaccini, A. R.	129	0.55	Zhang, Y.	162	0.51
Hubbell, J. A.	11	2.12	Kim, S. H.	54	0.69	Khademhosseini, A.	123	0.53	Mano, J. F.	162	0.51
Vunjak-Novakovic, G.	10	1.93	Van Blitterswijk, C. A.	53	0.67	Wang, L.	122	0.52	Okano, T.	153	0.48
Germain, L.	9	1.73	Jansen, J. A.	52	0.66	Wang, J.	117	0.50	Ramakrishna, S.	152	0.48
Martin, I.	9	1.73	Okano, T.	52	0.66	Wang, Y.	117	0.50	Langer, R.	149	0.47
Ito, Y.	9	1.73	Kim, B. S.	51	0.65	Ramakrishna, S.	111	0.48	Kim, S. H.	143	0.45
Burmester, G. R.	9	1.73	Kaplan, D. L.	51	0.65	Li, Y.	111	0.48	Wang, J.	142	0.45
Auger, F. A.	9	1.73	Laurencin, C. T.	50	0.63	Lee, J. H.	99	0.43	Khademhosseini, A.	141	0.45
Ma, P. X.	8	1.54	Khang, G.	50	0.63	Zhang, L.	99	0.43	Wang, Y.	138	0.44
Kim, B. S.	8	1.54	Ueda, M.	50	0.63	Zhang, X.	97	0.42	Wang, L.	136	0.43
VunjakNovakovic, G.	8	1.54	Mooney, D. J.	49	0.62	Okano, T.	95	0.41	Vunjak-Novakovic, G.	133	0.42
Healy, K. E.	8	1.54	Yamato, M.	47	0.60	Kim, J. H.	90	0.39	Li, Y.	128	0.40
Yaszemski, M. J.	8	1.54	Reis, R. L.	47	0.60	Kim, S. H.	89	0.38	Hutmacher, D. W.	124	0.39
Vacanti, C. A.	8	1.54	Hutmacher, D. W.	45	0.57	Liu, J.	86	0.37	Khang, G.	123	0.39
Bujia, J.	8	1.54	Anseth, K. S.	45	0.57	Mikos, A. G.	85	0.37	Athanasiou, K. A.	121	0.38

Table 4. Analysis of documents referred to TE by authorship from 1991 to 2016. An inversely proportional exponential relation between authors and contributions (Lotka’s law of scientific productivity) reveals Rui L. Reis, Dave L. Kaplan and Antonios G. Mikos as the most productive authors. A: Author name; C: Document count; %: Percentage of documents.

Title	Authors	Year	Journal	Reference	Cites count
Tissue engineering.	Langer, R & Vacanti, JP	1993	*SCIENCE*	260(5110):920-26	**5631**
Multilineage cells from human adipose tissue: Implications for cell-based therapies.	Zuk, PA; et al.	2001	*TISSUE ENGINEERING*	7(2):211-28	**3539**
Scaffolds in tissue engineering bone and cartilage.	Hutmacher, DW	2000	*BIOMATERIALS*	21(24):2529-43	**2395**
Silk-based biomaterials.	Altman, GH; et al.	2003	*BIOMATERIALS*	24(3):401-16	**1533**
Porous scaffold design for tissue engineering.	Hollister, SJ	2005	*NATURE MATERIALS*	4(7):518-24	**1399**
Electrospun nanofibrous structure: A novel scaffold for tissue engineering.	Li, WJ; et al.	2002	*JOURNAL OF BIOMEDICAL MATERIALS RESEARCH*	60(4):613-21	**1418**
Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study.	LeBlanc, K; et al.	2008	*LANCET*	3(2):232-38	**1314**
Wnt proteins are lipid-modified and can act as stem cell growth factors.	Willert, K; et al.	2003	*NATURE*	423(6938):448-52	**1254**
Electrospinning of collagen nanofibers.	Matthews, JA; et al.	2002	*BIOMACROMOLECULES*	371(9624):1579-86	**1247**
A biodegradable nanofiber scaffold by electrospinning and its potential for bone tissue engineering.	Yoshimoto, H; et al.	2003	*BIOMATERIALS*	24(12):2077-82	**1164**

Table 5. Top-cited documents referred to TE by citation count from 1991 to 2016. Seminal article by R. Langer and J.P. Vacanti received 5631 cites being the most relevant document in terms of citation count during the period studied.

cellular matrices are among the three most productive areas of TE as indicated in previous bibliometric studies [17]. The slightly decrease of the document percentage belonging to life sciences and biomedicine, including health and clinical applications could be related to the increase of regulatory rules implemented for clinical application of TE products. This suggests an important focus of research for the future. Furthermore, we consider that the analysis of keywords of each retrieved document could provide more valuable results about the future on the directions of research fields. In this sense, we are developing some new methodologies to perform science mapping analysis (SMA) on keywords in further research.

Our results suggest that multidisciplinarity of TE is not a static character but a dynamic process in which several categories participate in a global effort to generate more biomimetic tissues to be applied as therapeutical substitutes in clinical medicine. It is important to point out that native tissues, as known by classical histology, are the models that should be taken into account for the generation of artificial tissues. In this sense, various TE clinical applications can be pointed out. For example, those related with TE and Hematology, TE and Cardiology and TE and Neurology.

The previously demonstrated contribution of physical sciences to TE implies that the systematic study of the physical properties of biomaterials demands a crescent attention by tissue engineers. In fact, Gurkan and Akkus studied the mechanical environment of bone marrow and they showed that the changes in mechanical and compositional microenvironment of bone marrow may affect the fate of resident stem cells *in vivo* which, in turn, may alter the homeostasis of bone in various common bone diseases [43]. The connection between TE and Cardiology is oriented to the development of tissue constructs capable to restore or improve cardiac function after myocardial infarction. Concerning this, Gálvez-Montón et al. have designed a neoinnervation and neovascularization process for TE scaffolds in myocardial infarcts [44]. Moreover, peripheral nerve injury continues to be an important difficulty for a wide range of patients with conditions such as diabetes, Guillain-Barré syndrome or iatrogenic causes. Associated with this, TE peripheral nervous emerged as a promising therapeutic tool. Thus, bioengineered nerve development and the evaluation of growing factors that enhance differentiation of stem cells through a neural lineage have been topics of intense research during TE evolution [45, 46].

Technology category is the most relevant as it is involved in more than 50% of global production since 1996 to nowadays. The main research areas in Technology are Materials Sciences and Engineering due to the central role that plays the development of an optimal scaffold which allows the growth and functionality of cells and its biocompatibility. The design of an appropriate scaffold is a key issue in the generation of a bioengineered tissue because it should replace the histological structure of the native stroma. Life Sciences and Biomedicine, represented by Cell Biology, Biotechnology and Applied Microbiology and Biochemistry and Molecular

Biology, appeared as a second cluster of knowledge. In this case, that fact could be explained by the relevance of cells and growing factors as pillars of the TE, together with the scaffold. In addition, the main journals regarding Histology and Tissue Biology are included in this category. However, the relative weight of Life Sciences and Biomedicine tend to decrease in the recent years, as well as Physical Sciences emerge as a complement not only for the scaffold development but also for the improvement of the whole artificial tissues. Research in physical properties, as biomechanics, optics, etc, on artificial tissues has strongly increased in recent years in order to provide with the more biomimetic characteristics to the new tissues.

Distribution of source titles correlated with the Bradford's law of scattering as a small group of journals reported the majority of the available documents. Bradford's nuclei can be defined as the group of journals that publish a 25% or a 50% of the global production. In this sense, a total of 8 journals encompass a 25% of TE-related documents representing the core journals of the discipline. According to the Bradford's law of scattering there are a vast majority of journals reporting less than 5 documents.

The previous study published by Dai et al. analyzed all available literature up to 2008, and found that all selected documents corresponded to 140 journals [17]. Here, a total of 2070 journals have reported at least one of the 31,859 scientific articles. However, up to 1380 journals (66.67%) have published less than 5 documents, being considered as minority sources and, thus, disposable. The results are in accordance with Bradford's law of scattering which postulates that most of documents reported in a specific area located in a minority of sources. Table 1 presents the 20 most productive journals (source titles are abbreviated) globally and by time ranges. Bold-typed in table 1 represents core journals at each range as determined by Bradford nuclei that cluster 25% of all documents. A total of 8 journals compose the core journals in TE, being Biomaterials, Journal of Biomedical Materials Research Part A and Tissue Engineering Part A the source of 15% of the corpus.

Results attending to 2009-2016 range are very similar to global results because of the exponential increase of scientific production that gathers 73.48% of articles in the last 7 years. 1991-1999 and 2000-2008 series show more reduced Bradford nuclei with only 3 core journals reporting 25% of documents. Biomaterials, as the most productive journal in all time series, reported more percentage of documents at the earlier stages of TE development, from 10.79% documents in 1991-1999, to 5.75% documents in 2009-2016. Similar results were obtained for Journal of Biomedical Materials Research whose production decreased from 10.02% in 1991-1999 to 5.33% in 2009-2016 (adding parts A and B). These results may not only imply the raise of documents per year, but also the emergence of a huge number of new journals, mainly during recent years.

According to country distribution involved in TE production our results showed that USA with institutions as Harvard University and University of California System and China with the Chinese Academy of Sciences and the Shangai Jiao Tong University were the most productive centers. Furthermore, an assessment of countries where manuscripts were generated revealed USA as the most important country in term of TE scientific production participating in 8782 documents (27.75%). Next origin country in production is China with 4836 documents (15.28%), followed by Germany (5.95 %), Japan (5.77%) and South Korea (5.13%). It is remarkable the increase trend of TE in Asiatic countries as China, producing from 0.19% of documents in 1991-1999 to 17.84% in 2009-2016; and South Korea, from 1.93% in 1991-1999 to 5.47% in 2009-2016. Table 2 summarizes a list of the 20 countries with the higher amount of journal articles and percentages. Global diversity is not only evident after studying source title but also country distribution as the number of countries with more than 10 documents was 4 (14.81%) in 1991-1999; 32 (60.38%) in 2000-2008 and 53 (63.86%) in 2009-2016 (data not shown). Harvard University (3.00%), University of California System (2.60%) and Massachusetts Institute of Technology (1.81%), all of them sited in USA, appeared as the institutions generating the greater number of articles based on TE. Together with Chinese Academy of Sciences (1.78%) and University of London (1.72%) constitute the top five centers on TE research and produce more than 10% of global production.

During the early stage of TE (1991-1999) there was a majority of American institutions that established the foundation of TE, in coexistence with some German and Japanese universities. From 2000 to nowadays, it can be observed a quick arise of Asiatic institutions as the Chinese Academy of Sciences, Shanghai Jiao Tong University or the National University of Singapore, being these among the 10 most productive institutions and mainly responsible of the development of TE as a research area. The appearance of asiatic countries is remarkable specially from 2000 to nowadays. These results suggest a correlation between the national investment on research and the document amount per country [47]. This correlation was not surprising from mainstream countries since this pattern has been reported in other scientific fields [13]. A summary of the more relevant filiation centers producing TE articles is shown in Table 3.

Similarly to research areas evaluation, an analysis of authorship showed a huge imbalance in the relevance of authors participating in TE. As Alfred J. Lotka postulated, the number of authors involved in x contributions follows an inverse-square law. In this study, an inversely proportional exponential relation was found between authors and contributions in which the number of authors decrease directly proportional to $1/x^2.4$ being x the number of documents. Particularly, 67,231 researchers have been detected as authors in any TE scientific article. Nonetheless, the vast majority of these participations are singular as there are 41,081 authors with a single participation. Even more, 0.3% of authors are involved in 50% of TE articles, which is a clear example Lotka's law of scientific productivity in which the number of authors and the number of contributions closely follows the function $y = 87120/x^2.4$ ($R^2 = 0.981$), meaning an inversely proportional exponential relation between authors and contributions.

In fact, twenty first most productive authors, detailed in Table 4, have participated of up to 10% of total articles from 1991 to 2016. Rui L. Reis, Dave L. Kaplan and Antonios G. Mikos are the most relevant authors when taking into account the whole corpus. During the first stages of TE development, Robert Langer was the most remarkable researcher with 8.09% authorship of all the publications during 1991-1999. From 2000 and beyond, TE exponentially increase and Antonios G. Mikos (1.13% of documents between 2000 and 2008) and Rui L. Reis (1.07% of documents between 2009 and 2016) appeared as the most productive researchers.

According to citation analysis it revealed an average citation of all articles in 27.26 citing articles per document, and the Hirsch-index was up to 266. Due to the huge amount of articles reported last years (73.48% of documents have been published during last 7 years), there are yet 35.00% of documents with less than 5 cites. This could be explained because of exponential growth of TE as 73.48% of total documents have been published during the last seven years. With respect to the most relevant reports, 5.39% documents accumulate more than 100 cites, 0.24% of total documents achieved more than 500 cites. Finally, the corpus of keystone papers, considered as articles with more than 1000 cites, is formed by 16 documents.

The most relevant article for TE gathers 5631 cites [2], which means that 17.24% as maximum of TE articles have cited it (assuming that only TE articles have cited it). A selection of the 10 top-cited TE articles is detailed in Table 5. In this sense, the most cited documents are considered landmarks as they supposed turning points in the evolution of TE. Multilineage differentiation of mesenchymal stem cells or electrospinning as a novel method for biomaterial orientation are considered milestones in the development of TE and thus original publications about these topics are among the ten top-cited documents. The most cited paper of TE is the seminal document of discipline published by Langer and Vacanti in 1993. In this article, it is defined the foundations of this discipline and future applications of therapy. It is considered the most relevant document of TE as almost one of each five documents cited it.

A remarkable change related to TE country production was shown here in comparison with the previous work by Dai et al. In this early study, it was concluded that TE literature mainly come from United States, England, Netherlands and Germany [17]. We have demonstrated here that the appearance of Asiatic countries is significant from 2000, being China the second most productive country. Finally, a common idea in medical literature that TE is still an emerging discipline should be forgotten. According to Gompertz model to predict the development of a discipline, TE is not an emerging area but a consolidating discipline [42].

In summary, bibliometric analysis is a valid tool for the study of the global trends and temporal evolution of a discipline like TE. In this milieu, this study represents a global analysis of the corpus of literature available nowadays. Results obtained related to research areas showed a high and increasing multidisciplinary role of TE as all the science and technology categories of knowledge converge their research efforts leading to the development of new applications for daily clinical practice. As reported in other scientific fields a great imbalance is patent as few authors, journals and countries are responsible of the majority of TE documents. Further analysis focused on the terminological evolution and identification of the most relevant concepts could provide an useful tool not only for the design of teaching strategies but also for promoting future avenues in tissue engineering research.

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Competing interests

All authors declare there is not any financial or personal relationship with organizations that could potentially be perceived as influencing the described research.

References

[1] G. T. Huang. A paradigm shift in endodontic management of immature teeth: conservation of stem cells for regeneration. *J Dent*, 36(6):379–86, 2008.

[2] R. Langer and J. P. Vacanti. Tissue engineering. *Science*, 260(5110):920–6, 1993.

[3] S. Parveen, K. Krishnakumar, and S. Sahoo. New era in health care: tissue engineering. *J Stem Cells Regen Med*, 1(1):8–24, 2006.

[4] J. Stanovici, L. R. Le Nail, M. A. Brennan, L. Vidal, V. Trichet, P. Rosset, and P. Layrolle. Bone regeneration strategies with bone marrow stromal cells in orthopaedic surgery. *Curr Res Transl Med*, 64(2):83–90, 2016.

[5] K. X. Ren, C. L. He, C. S. Xiao, G. Li, and X. S. Chen. Injectable glycopolypeptide hydrogels as biomimetic scaffolds for cartilage tissue engineering. *Biomaterials*, 51:238–249, 2015.

[6] H. Debels, M. Hamdi, K. Abberton, and W. Morrison. Dermal matrices and bioengineered skin substitutes: a critical review of current options. *Plast Reconstr Surg Glob Open*, 3(1):e284, 2015.

[7] N. Cuende and A. Izeta. Clinical translation of stem cell therapies: a bridgeable gap. *Cell Stem Cell*, 6(6):508–12, 2010.

[8] O. Ellegaard and J. A. Wallin. The bibliometric analysis of scholarly production: How great is the impact? *Scientometrics*, 105(3):1809–1831, 2015.

[9] J. A. Wallin. Bibliometric methods: Pitfalls and possibilities. *Basic Clin Pharmacol Toxicol*, 97(5):261–275, 2005.

[10] J. Choi, J. S. You, Y. S. Joo, T. Kong, D. R. Ko, and S. P. Chung. A bibliometric analysis of research productivity of emergency medicine researchers in south korea. *Clin Exp Emerg Med*, 3(4):245–251, 2016.

[11] T. Ellul, N. Bullock, T. Abdelrahman, Agmt Powell, J. Witherspoon, and W. G. Lewis. The 100 most cited manuscripts in emergency abdominal surgery: A bibliometric analysis. *Int J Surg*, 37:29–35, 2017.

[12] T. Gagne, J. Lapalme, and D. V. McQueen. Multidisciplinarity in health promotion: a bibliometric analysis of current research. *Health Promot Int*, 2017.

[13] L. L. Li, G. H. Ding, N. Feng, M. H. Wang, and Y. S. Ho. Global stem cell research trend: Bibliometric analysis as a tool for mapping of trends from 1991 to 2006. *Scientometrics*, 80(1):39–58, 2009.

[14] Q. H. Pu, Q. J. Lyu, and H. Y. Su. Bibliometric analysis of scientific publications in transplantation journals from mainland china, japan, south korea and taiwan between 2006 and 2015. *Bmj Open*, 6(8):7, 2016.

[15] W. M. Sweileh, N. Y. Shraim, S. W. Al-Jabi, A. F. Sawalha, A. S. AbuTaha, and S. H. Zyoud. Bibliometric analysis of global scientific research on carbapenem resistance (1986-2015). *Ann Clin Microbiol Antimicrob*, 15:11, 2016.

[16] M. Y. Wei, W. M. Wang, and Y. F. Zhuang. Worldwide research productivity in the field of spine surgery: a 10-year bibliometric analysis. *Eur Spine J*, 25(4):976–982, 2016.

[17] G. Dai, K. H. Yang, and Q. H. Li. [bibliometric analysis on tissue engineering research literatures]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*, 14(5):308–10, 2000.

[18] J. A. Basualdo, M. S. Grenovero, E. Bertucci, and N. B. Molina. Bibliometric analysis of scientific literature on intestinal parasites in argentina during the period 1985-2014. *Rev Argent Microbiol*, 48(2):171–9, 2016.

[19] P. Royle and N. Waugh. Macular disease research in the united kingdom 2011-2014: a bibliometric analysis of outputs, performance and coverage. *BMC Res Notes*, 8:833, 2015.

[20] J. Ruiz-Saenz and M. Martinez-Gutierrez. Virology research in a latin american developing country: a bibliometric analysis of virology in colombia (2000-2013). *J Infect Dev Ctries*, 9(11):1226–1237, 2015.

[21] F. H. Chokshi, J. Kang, S. Kundu, and M. Castillo. Bibliometric analysis of manuscript title characteristics associated with higher citation numbers: A comparison of three major radiology journals, ajnr, ajr, and radiology. *Curr Probl Diagn Radiol*, 45(6):356–360, 2016.

[22] T. Shamim. Bibliometric analysis of the dental science articles published in the iranian journal of medical sciences (ijms) from 2002 to 2015 over a 14-year period. *Iran J Med Sci*, 42(1):106–107, 2017.

[23] D. Zeleznik, H. B. Vosner, and P. Kokol. A bibliometric analysis of the journal of advanced nursing, 1976-2015. *J Adv Nurs*, 73(10):2407–2419, 2017.

[24] S. A. Azer. Top-cited articles in problem-based learning: A bibliometric analysis and quality of evidence assessment. *J Dent Educ*, 81(4):458–478, 2017.

[25] M. E. O'Keffe, T. N. Hanna, D. Holmes, O. Marais, M. F. Mohammed, S. Clark, P. McLaughlin, S. Nicolaou, and F. Khosa. The 100 most-cited original articles in cardiac computed tomography: A bibliometric analysis. *J Cardiovasc Comput Tomogr*, 10(5):414–423, 2016.

[26] A. Tahim, K. Patel, C. Bridle, and S. Holmes. The 100 most cited articles in facial trauma: A bibliometric analysis. *J Oral Maxillofac Surg*, 74(11):2240 e1–2240 e14, 2016.

[27] Y. G. Zhang, J. Huang, and L. Du. The top-cited systematic reviews/meta-analyses in tuberculosis research a prisma-compliant systematic literature review and bibliometric analysis. *Medicine*, 96(6):5, 2017.

[28] C. G. Daughton. Pharmaceuticals and the environment (pie): Evolution and impact of the published literature revealed by bibliometric analysis. *Sci Total Environ*, 562:391–426, 2016.

[29] A. M. Muller, P. Ansari, N. A. Ebrahim, and S. Khoo. Physical activity and aging research: A bibliometric analysis. *J Aging Phys Act*, 24(3):476–83, 2016.

[30] L. Perrier, D. Lightfoot, M. R. Kealey, S. E. Straus, and A. C. Tricco. Knowledge synthesis research: a bibliometric analysis. *J Clin Epidemiol*, 73:50–57, 2016.

[31] R. Khosravi, K. S. Miller, C. A. Best, Y. C. Shih, Y. U. Lee, T. Yi, T. Shinoka, C. K. Breuer, and J. D. Humphrey. Biomechanical diversity despite mechanobiological stability in tissue engineered vascular grafts two years post-implantation. *Tissue Eng Part A*, 21(9-10):1529–38, 2015.

[32] R. Katari, A. Peloso, and G. Orlando. Tissue engineering and regenerative medicine: semantic considerations for an evolving paradigm. *Front Bioeng Biotechnol*, 2:57, 2014.

[33] A. J. Salgado, J. M. Oliveira, A. Martins, F. G. Teixeira, N. A. Silva, N. M. Neves, N. Sousa, and R. L. Reis. Tissue engineering and regenerative medicine: past, present, and future. *Int Rev Neurobiol*, 108:1–33, 2013.

[34] V. H. Lee, J. J. Hew, and S. P. Loke. Evaluating and comparing ten-year (2006-2015) research performance

between malaysian public and private higher learning institutions: a bibliometric approach. *International Journal of Innovation and Learning*, 23(2):145–165, 2018.

[35] G. Abramo, C. A. D'Angelo, and A. Caprasecca. Allocative efficiency in public research funding: Can bibliometrics help? *Res Policy*, 38(1):206–215, 2009.

[36] S. R. Rosas, J. M. Kagan, J. T. Schouten, P. A. Slack, and W. M. Trochim. Evaluating research and impact: a bibliometric analysis of research by the nih/niaid hiv/aids clinical trials networks. *PLoS One*, 6(3):e17428, 2011.

[37] G. Lewison and G. Paraje. The classification of biomedical journals by research level. *Scientometrics*, 60(2):145–157, 2004.

[38] F. Narin, G. Pinski, and H. H. Gee. Structure of biomedical literature. *J Am Soc Inform Sci*, 27(1):25–45, 1976.

[39] G. M. Weber. Identifying translational science within the triangle of biomedicine. *J Transl Med*, 11:126, 2013.

[40] S. Asgary, S. Sabbagh, A. S. Shirazi, M. Ahmadyar, A. Shahravan, and M. S. Akhoundi. Pubmed-indexed dental publications from iran: A scientometric study. *J Dent (Tehran)*, 13(3):157–167, 2016.

[41] D. D. S. Price. A general theory of bibliometric and other cumulative advantage processes. *J Am Soc Inform Sci*, 27(5):292–306, 1976.

[42] B Gompertz. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos Trans Royal Soc*, 115:513–583, 1825.

[43] U. A. Gurkan and O. Akkus. The mechanical environment of bone marrow: a review. *Ann Biomed Eng*, 36(12):1978–91, 2008.

[44] C. Galvez-Monton, M. T. Fernandez-Figueras, M. Marti, C. Soler-Botija, S. Roura, I. Perea-Gil, C. Prat-Vidal, A. Llucia-Valldeperas, A. Raya, and A. Bayes-Genis. Neoinnervation and neovascularization of acellular pericardial-derived scaffolds in myocardial infarcts. *Stem Cell Res Ther*, 6:108, 2015.

[45] B. Battiston, S. Raimondo, P. Tos, V. Gaidano, C. Audisio, A. Scevola, I. Perroteau, and S. Geuna. Chapter 11: Tissue engineering of peripheral nerves. *Int Rev Neurobiol*, 87:227–49, 2009.

[46] X. Gu, F. Ding, and D. F. Williams. Neural tissue engineering options for peripheral nerve regeneration. *Biomaterials*, 35(24):6143–56, 2014.

[47] G. A. Crespi and A. Geuna. An empirical study of scientific production: A cross country analysis, 1981-2002. *Res Policy*, 37(4):565–579, 2008.