Publication trends and knowledge maps of global translational medicine research

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Abstract

Translational medical research literatures have increased rapidly in last decades and there have been fewer attempts or efforts to map global research context of translational medical related research. The main purpose of this study is to evaluate the global progress and to assess the current quantitatively trends on translational medical research by using a scientometric approach to survey translational medicine related literatures in Science Citation Index Expanded (SCI-E), Social Science Citation Index (SSCI) and PubMed database from 1992 to 2012. The scientometric methods and knowledge visualization technologies were employed in this paper. The document types, languages, publication patterns, subject categories, journals, geographic and institutional distributions, top cited papers, and the distribution of keywords as well as MeSH terms were thoroughly examined.

Translational medicine research has increased rapidly over past 20 years, most notably in the last four years. In total, there are currently 3,627 research articles in 1,062 journals listed in 91 SCI-E subject categories. The top 20 productive countries and institutes were analyzed herein, where 11 key papers in translational medical research and research foci were identified. Research outputs descriptors have suggested that the presence of a solid development in translational medical research, where research in this field has mainly focused on experimental medicine, general internal medicine, and medical laboratory technologies. All these outcomes have been concentrated in several journals such as *Translational Research, Translational Oncology, Translational Stroke Research,* and *Translational Neuroscience*. G7 countries make up the leading nations for translational medical research, where the center is located in USA. American institutions have made great advances in paper productions, citations, and cooperation, with overall great strengths and good development prospects. Moreover, the evolution pathway of translational medical research has been summarized as bellows: problems emerged, causes analyzed, challenges faced and solutions proposed, translational medical research programs been formally established, theoretical and applied research, all of which was in full swing. During this process, neoplasms and genomics, interdisciplinary communication between academic medical centers/institutes, drug design and development, cardiovascular and brain diseases, and even biomedical research have been identified as mainstream topics in translational medical research fields.

Keywords

Translational medical research, Scientometric, Research trend, Web of Science, PubMed, Knowledge mapping.

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Introduction

Although improving health is the common objective of basic life science and biomedical research, this goal has not been well achieved as often as desired or needed. One well-designed study found that less than 25% of highly promising biomedical discoveries resulted in a published randomized clinical trial and less than 10% were established in clinical practice within last 20 years (Contopoulos-Ioannidis DG, 2003). Moreover, medications and treatments are not administered universally appropriate in clinical practice. Well-known examples include the administration of beta blockers after myocardial infarction (MI) or lipid screening and cholesterol-lowering agents in coronary artery disease(Freemantle N, 1999; McBride P, 1998). To improve human health, scientific discoveries must be translated into practical applications and such discoveries typically begin at "the bench" with basic research in which scientists study the disease at a molecular or cellular level for the progress to the clinical level, or the patient's "bedside." Translational research has proven to be a powerful process that drives the clinical research engine.

The term "translational medical research" (also known as translational medical science, translational research or translational research, medical) was introduced as a Medical Subject Headings (MeSH) term in 2009. E. Zerhouni proposed in a National Institutes of Health (NIH) roadmap clearly that the main purposes of translational medical research are to translate basic medical research results into clinical practicing techniques or drugs effectively (Marincola, 2003; Zerhouni, 2005). Before the idea of translational research was put forward formally by D. W. Choi in 1992 as the standard for cancer prevention and control, the "bench-bedside interface" model had been proposed by the *New England Journal of Medicine* in 1968 (Editor 1968). Although the term "translational medical research" appeared as early as 1996 (Geraghty, 1996), there were relatively few references to this term in medical literatures during the 1990s, and most references involved in the research about cancer. While literatures today includes a plethora of attempts in various fields to define the term(Rubio et al., 2010), the definition of translational research is not yet established up until now.

In order to promote the development of translational medical research, numerous large-scale international symposia and conferences have been held all over the world. At the same time many key journals have opened special columns for translational medical research. *Science Translational Medical Research* (*STMR*) and *American Journal of Translational Research* founded in 2009, in company with *Journal of Translational Medical Research*, *Translational Research,* and *Clinical and Translational Science*, have constituted the information network hub of translational medical research. Moreover, *STMR,* founded as a sub-publication of *Science* in 2009, also established the Excellence in Translational Medical Research Award and the Bedside-to-bench Award to recognize and encourage the growing number of scholars engaged in translational medical research(Brander et al., 2006). In addition, NIH launched the Clinical and Translational Science Awards (CTSAs) to find innovative ways collectively to speed up discoveries and advance such science as a strategy to help increasing the safety and efficiency of translational research in 2006 (Website 2012). In the same year, translational research also became a centerpiece of the European Commission for Health research when UK established numerous translational research centers (Woolf, 2008). After 2006, many other countries and regions started to establish translational research centers. People's Republic of China, for example, has established more than fifty translational medical research centers at this time.

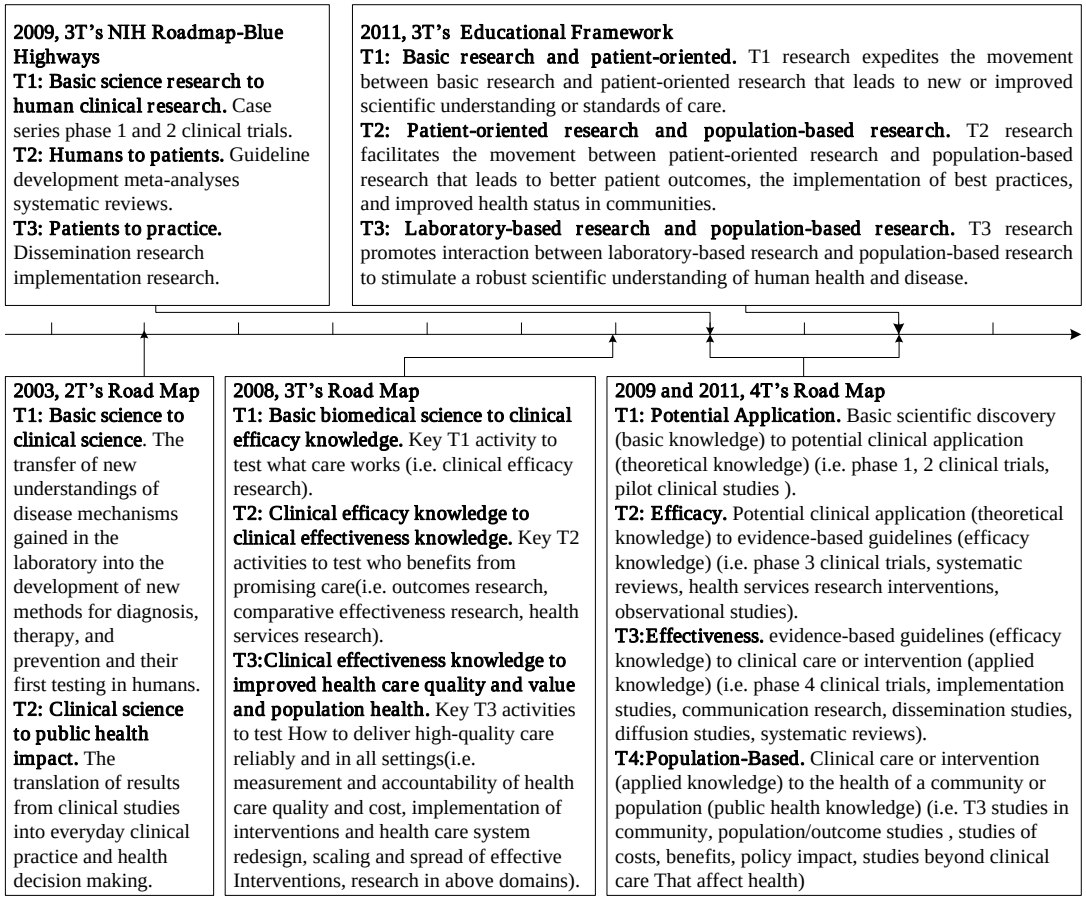

Figure 1. The evolution pathway of translational medical research modes

In a recent announcement about applying for the Clinical and Translational Science Awards (CTSAs), NIH offered the following definition and description as "translational research includes two areas of translation that one is the process of applying discoveries generated during research in the laboratory and in preclinical studies, to the development of trials and studies in humans; the second area of translation concerns research aimed at enhancing the adoption of best practices in the community." (Rubio et al., 2010). According to this definition, translational research is a part of a unidirectional continuum in which research findings are moved from the researcher's bench to the patient's bedside and community at large.

In the continuum, the first stage of translational research (T1) transfers knowledge from basic research to clinical research while the second stage (T2) transfers most findings from clinical studies or clinical trials to practice settings and communities, where the findings are expected to improve health care services. Translational medical research has also formed many "T" modes during the development periods, such as 2T, 3T and 4T modes as Figure 1 shown.

The Institute of Medicine Clinical Research Roundtable described the current terminology and model of translational research for the first in 2003 as a two-phase process of research progressing in which they also identified ''translational blocks'' between these steps as shown in Figure 1. This mode, highly aligned with the NIH definition, portrays T2 as one step that the translation of new knowledge into clinical practice-but the process is rarely that simple. Westfall et al. redrew this mode to include a

third step (T3) as practice-based research, which is often necessary before distilled knowledge (e.g., systematic reviews and guidelines) can be implemented into practice (Westfall et al., 2007). Thus the second phase of translation was later subdivided to create a model of the translational phases (Drolet and Lorenzi, 2011).

The most influential translation model is the 3T's Road Map proposed by D. Dougherty and P. H. Conway in 2008 (Dougherty and Conway, 2008). In this mode, basic science and its translation into clinical research (T1) are only the beginning of the process toward high-quality, effective and safe health care delivery. Meanwhile, members of the Evaluation Committee of the Association for Clinical Research Training (ACRT) reviewed current definitions of translational research and proposed an operational definition to use in the 3T's educational framework (Rubio et al., 2010) that offer a guide to institutions in developing processes of program evaluation. The most current used translation mode in the literature expounds the 4T's process (Drolet and Lorenzi, 2011) as explained in Figure 1.

Although these modes have improved on prior modes in providing greater detail, the terminology remains indistinct to both researchers and physicians. In numerous references, the four T terms (T1, T2, T3 and T4) are used indiscriminately to describe translation obstacles, translation steps, translational activities or translational research. B. C. Drolet and N. M. Lorenzi thus proposed a novel model called the Biomedical Translation Continuum to describe and evaluate the process of bringing basic life science findings to public health interventions (Drolet and Lorenzi, 2011). This mode has been very useful for practicing physicians and other researchers who do not follow the ever-changing literature on translation.

Despite the importance and high growth rate of translational medical research is both in theory and practice, there have been few attempts or efforts to map global translational medical research related context. The main purpose of this study is therefore to evaluate the global progress and to assess of current research trends on translational medical research quantitatively. A comprehensive scientometric analysis and substantial discussion of research progress in translational medical research were provided so that specifically attempts was employed to (1) summarize significant publication patterns in translational medical research with basic statistics as well as advanced analytics, (2) evaluate research performance from multiple perspectives such as published year, subject categories, journals, countries/regions as well as institutes (Enachescu and Postelnicu, 2003; Faba-Perez et al., 2003) and (3) present the evolution pathway and research foci of international translational medical research. Moreover, citation data were used as a scientometric tool to indicate the intellectual impact of the research outputs. The results provide evidence of the current status and future trends in translational medical research all over the world, as well as clues to the impact of this hot topic, thus helping scholars understanding the panorama of global translational medical research and predict the dynamic directions of such research.

Data and methods

ℓ Data sources

Due to WoS database is the most authority one used to study the publications in most topics for a given subject, but for the topics from medical science the PubMed is the most used data source. In this papers, both WoS and PubMed database were investigated to get an reflection of the publications, and then the most influence paper data was selected to study the evolution pathway and research foci further.

As the Web of Science (WoS) databases have been identified as the most appropriate for the objectives of investigation, so all publications on translational medical research was collected within the online version of Science Citation Index Expanded (SCI-E) and Social Science Citation Index (SSCI) published by Thomson Router, operated by Thomson Scientific, Philadelphia, PA, USA(Chen et al., 2007). The main advantage of the WoS journals is that they constitute the most important (in terms of impact) journals in the world (Boyack et al., 2005; Pouris and Pouris, 2011). The relevant articles were extracted using text-supplied keywords from the National Library of Medicine's Medical Subject Headings thesaurus. Identification of translational medical research articles was accomplished by searching titles, author-supplied abstracts and texts through ''relevant terms''. The relevant translational medical research terms include: "Medical Research, Translational", "Research, Translational Medical", "Translational Research, Medical", "Medical Translational Research", "Research, Medical Translational", "Translational Research", "Research, Translational", "Translational Researches", "Translational Medical Science", "Medical Science, Translational", "Medical Sciences, Translational", "Science, Translational Medical", "Sciences, Translational Medical", "Translational Medical Sciences", "Translational Medicine", and "Medicine, Translational". However, the benefits of using scientometric searching terms are always debatable. There are two criteria commonly used for analysis of scientometric search terms, that of recall and precision. Recall refers to the ability of the term to minimize the number of relevant documents missed. Precision refers to the ability of the search term to minimize the number of irrelevant records retrieved.

In order to improve the two criteria, papers in journals whose name contains "translat*" are included, and the papers which do not belong to medicine related subjects are excluded. The search strategy is thus arranged as *TS = ("Translat* Medic*" OR "Translat* Research*") OR SO = (Translat*)) NOT (WC =(Information Science Library Science OR Education Educational Research OR Education Special OR Social Issues OR Social Work OR Computer Science Interdisciplinary Applications OR Social Sciences Interdisciplinary OR Sport Sciences OR Statistics Probability OR Plant Sciences OR Zoology OR Computer Science Information Systems OR History Philosophy of Science OR Ethics OR Computer Science Artificial Intelligence OR Nuclear Science Technology OR Language Linguistics OR Linguistics).* Based on the former searching strategy, a total of 5,451 publications were identified in SCI-E and SSCI databases and 2,952 publications were obtained in PubMed database within all-time spans.

ℓ Methodologies

As seen by readers first, the title of an article has the core information that authors would like to express (Lou and Lin, 2012). As author keyword analysis offers information about research trends from the view of researchers, it has proved to be important for monitoring the development of science (Li et al., 2009). Keywords Plus supplies additional search terms extracted from the titles of articles cited by authors in their bibliographies and footnotes (Garfield, 1990). So the topic of papers can be obtained from the title-words, author keywords, and Keywords Plus by cluster analysis. Because through automatic keyword clustering, CiteSpace can also identify the major research fields and hot topics in translational medical research and thus employed in this paper. Based on the map of critical node literature in Citespace software, clicking "cluster" with the source as "label clusters with title words", the clusters could be identified. The clusters whose size is greater than others are displayed with their tf * idf (inverse document frequency algorithm) weighted values in this paper.

Following the best international practices, evaluative scientometrics was selected for this study. Scientometrics is a method by which the state of science and technology can be observed through the overall production of scientific literatures at a given level of specialization. This tool provides an approach for situating a country in relation to the world, an institution in relation to a country and individual scientists in relation to their peers. Bibliometric indicators are equally suitable for macro-analysis (e.g., a given country's share in global output of scientific literature over a given period) and micro-studies (e.g., a specified institute's role in producing articles in a particular field or specialty of science) (Pouris and Pouris, 2011). The Thomson Data Analyzer (TDA) (Wang and Pan, 2010), HistCite (Lucio-Arias, 2007), VOSviewer (van Eck and Waltman, 2010) and CiteSpace (Cobo et al., 2011) software were employed to analyze the publications for knowledge mapping.

To present more visual features for the evolution pathway of translational medical research, CiteSpace software was employed to construct a co-citation network of the references. CiteSpace uses a time-slicing mechanism to generate a synthesized panoramic network visualization based on a series of snapshots of the evolving network across consecutive time slices. The quality of the visualized network is promising: intellectually significant publications tend to have topologically unique features. In this sense, some salient intellectual turning points (nodes) are identified, and used to describe the evolving network of translational medical research from theory to practice. The centrality of a node is a graph-theoretical property that quantifies the importance of the node's position in a network. In the visual network map, the Freeman's betweenness centrality metric is used to highlight potential pivotal points, which is represented by the thickness of a red-purple ring around a node within a tree-ring of citations history, and also by the front size of labeled publication names. The radius size of the citation tree-ring represents the citation frequency in corresponded dataset (Chen and Guan, 2011). In order to improve the clarity of a visualized evolution network, a simplified network by pruning (i.e., link reduction, or network scaling) was used in this work. Here, a topology-based approach instead of a threshold-based approach is chosen for a more extensive consideration of intrinsic topological properties. In this study, pathfinder network scaling instead of minimal spanning trees was employed in order to preserve the chronological growth patterns in co-citation networks.

Results and discussion

ℓ Document types and languages

There are 5,451 total translational medical research related papers used in this study from the SCI-E and SSCI databases, including 13 document types (Campanario et al., 2011). There are 3,267 research articles, which comprise 59.9% of the total productions, followed by reviews (1,297; 23.8%), editorial material (697; 12.8%), meeting abstracts (343; 6.3%), proceedings papers (296; 5.4%), book chapters (144; 2.6%), letters (56; 1.0%), and news item (53; 0.9%). Other document types with fewer papers were neglected. Following the conventions used in other scientometric studies, further analysis to articles was restricted, which are peer-reviewed and represent original scientific development. Publications of all other types were thus removed from the analysis for the rest in this article.

As for publishing language, 3,197 or 97.9% of the 3,267 journal articles are written in English. This data confirmed that English is the prevalent academic language, and most SCI-E and SSCI indexed journals are published in English. Other publication languages include German (32; 1.0%), French (21; 0.6%), Japanese (7; 0.2%), Spanish (6; 0.2%), Chinese (1; 0.03%), Croatian (1; 0.03%), Finnish (1; 0.03%) and Italian (1; 0.03%).

ℓ Global Publication outputs

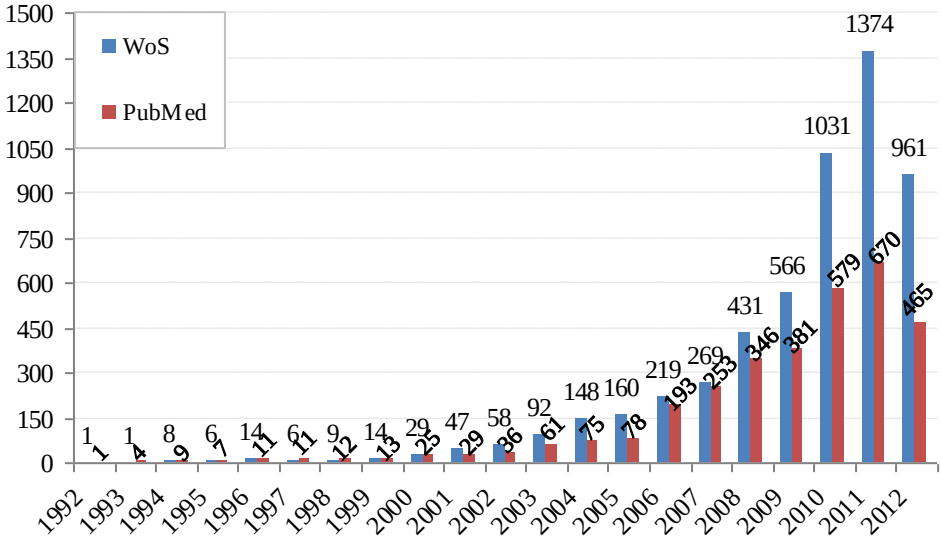

Figure 2. Translational medical research-related publications in WoS & PubMed (1992 to 2012)

The publication trends of annual papers in translational medical research from 1992 to 2012 were shown in Figure 2. It can be seen from Figure 2 that not many researchers paid their attentions to translational medical research published before 2000 and only a few papers published and little proceedings reported the progress of related work. Both WoS and PubMed's annual number of publications have grown exponentially, however, especially after 2006. During the past decades, WoS articles on translational medical research have been produced in a range from one in 1992 to approximately 1,400 in 2011. Meanwhile, PubMed papers on translational medical research exceeded 600 papers in 2011. Due to the limitation of the retrieval time, the number of papers in 2012 is partial and thus not adopted for analysis in this paper below.

Due to the translational medicine research is an emerging research field, the publication trend of it is so different from other general medicine researches such as tropical medicine. The production of translational medicine research boosted in recent years after the term introduced, while in other medicine research the publication trend is steady relatively for years. The tropical medicine or health are just good case in this situation.

ℓ Subject categories of papers

Table1. Top 10 productive WoS subject categories on translational medical research, 1992-2011

No.	SCI Subject Category	1992-1996	1997-2001	2002-2006	2007-2011	TP	%
1	Research Experimental Medicine	0	7	60	527	686	21.19
2	General Internal Medicine	2	8	77	440	605	18.69
3	Medical Laboratory Technology	0	2	39	342	444	13.72
4	Oncology	13	25	80	294	439	13.56
5	Neurosciences Neurology	3	4	29	278	408	12.60
6	Cell Biology	0	4	20	146	198	6.12

7	Public Environmental Occupational Health	3	7	34	111	181	5.59
8	Psychiatry	1	8	13	103	173	5.34
9	Health Care Sciences Services	1	5	28	109	161	4.97
10	Pharmacology Pharmacy	1	6	19	107	158	4.88

TP: number of articles and %: percentage of articles from different subject categories in total articles.

Based on the classification of subject categories in the Journal Citation Report (JCR) of WoS, the publications output data of translational medical research was distributed in 91 subject categories during the last two decades. The top 10 productive subject categories as all branches of medical science, are shown in Table1.

Table1 shows that translational medical research was mainly located in fields of basic clinical science (including research experimental medicine, medical laboratory technology, and cell biology) and clinical medical science (including general internal medicine, oncology, neurosciences neurology, and psychiatry), where pharmacology and pharmacy also played an important role too. In addition, increasingly more studies have focused on public health science, such as public environmental occupational health and health care sciences services, where investigators have studied factors and interventions that influence the health of populations. This table indicates that public health research (T3 and T4 research) has become an important part of translational medical research.

Table1 also indicates that research in the top 10 fields above began relatively early and increased slowly before 2006, especially in oncology. The period of rapid growth after 2006 may be related to the progress from CTSAs and the OSCHR programs, which support translation research. The translational medical research in the subjects of oncology occupied a dominant position in the earlier stages, while study of research experimental medicine, general internal medicine, and medical laboratory technology has gradually exceeded that of oncology in the past four years. Meanwhile, the number of scientific articles per category has exhibited a trend of rapid growth during the last decade, indicating that translational medical research is in a stage of rapid development stage and subsequently needs more efforts.

ℓ Core Journals of publication

Table2. Top 11 most productive WoS journals on translational medical research

No.	Journal	TP	%	LCS	LCS/t	GCS	GCS/t
1	*Translational Research*	418	12.80	48	10.1	2675	609.09
2	*Translational Oncology*	141	4.30	17	4.73	832	230.58
3	*Translational Stroke Research*	110	3.40	13	4.83	151	68.17
4	*Translational Neuroscience*	107	3.30	7	2.5	51	20.17
5	*Science Translational medical research*	80	2.40	0	0	185	79.17
6	*Translational Psychiatry*	80	2.40	0	0	54	32.00
7	*CTS-Clinical And Translational Science*	37	1.10	11	3.58	62	23.25

8	*Clinical Cancer Research*	28	0.90	33	6.42	821	118.33
9	*Diabetes Care*	28	0.90	97	14.01	550	94.34
10	*Neuroendocrine Immunology In Rheumatic Diseases: Translation From Basics To Clinics*	28	0.90	0	0	198	66.00
11	*PLoS ONE*	28	0.90	0	0	222	60.70

TP: number of articles; %: percentage of articles; LCS, Local Citation Score, which is the number of times cited by other papers in the local collection; LCS/t is the average value of LCS in a year; GCS, Global Citation Score, which is the citation frequency based on the full WoS count at the time the data was downloaded; GCS/t is the average value of GCS in a year.

In JCR 2011, 13,265 journals were listed as SCI-E journals and 4,554 journals were listed as SSCI journals. Translational medical research output was published in 1,062 journals, where the top 11 journals with more than 25 articles are displayed in Table2. There was a high concentration of translational medical research publications in these top journals, where approximately one third of the articles are found in these most productive journals, a phenomenon that follows the Bradford's law (Wang and Wang, 1998) and is consistent with observation in other fields. These top 11, or 1.0% out of the 1,062 journals, had published 1,085 or 33.3% of the total 3,267 articles and received 5, 801 or 19.3% of the total 30,031 citations.

Major publication outlets of translational medical research include *Translational Research, Translational Oncology, Translational Stroke Research,* and *Translational Neuroscience*. *Translational Research, Translational Oncology* and *Clinical Cancer Research* ranked top three in both GCS and GCS/t. Moreover, *Diabetes Care* had the highest LCS and LCS/t, followed by *Translational Research*. *Translational Research,* supported by the CTSA and renamed from the *Journal of Laboratory and Clinical Medicine* in 2006, is therefore the most important journal in translational medical research. There were only two papers related to translational medical research published in *Translational Research* before its name was changed, when it became devoted to the topic.

ℓ Countries of publication and collaboration

Table3. Top 20 most productive countries/territories of WoS articles during 1992–2011

No.	Country	TP	%	LCS	GCS	AGCS
1	USA	1953	59.80	673	21603	11.06
2	UK	238	7.30	31	2032	8.54
3	Germany	221	6.80	23	1695	7.67
4	Canada	195	6.00	40	2628	13.48
5	Italy	134	4.10	12	1611	12.02
6	Japan	120	3.70	21	771	6.43
7	The Netherlands	109	3.30	21	826	7.58
8	Peoples R China	93	2.80	6	474	5.10
9	France	91	2.80	11	490	5.38

10	Australia	85	2.60	5	522	6.14
11	Spain	84	2.60	15	1159	13.80
12	Switzerland	72	2.20	10	1216	16.89
13	Belgium	42	1.30	10	368	8.76
14	Croatia	42	1.30	1	10	0.24
15	Sweden	42	1.30	3	134	3.19
16	Austria	39	1.20	6	379	9.72
17	Taiwan	35	1.10	2	201	5.74
18	Brazil	31	0.90	2	149	4.81
19	Israel	31	0.90	3	241	7.77
20	Norway	30	0.90	2	205	6.83

TP number of articles; %: percentage of articles; LCS, Local Citation Score, is the number of times cited by other papers in the local collection; GCS, Global Citation Score, is the citation frequency based on the full Web of Science count at the time the data was downloaded; AGCS is the average citation frequency of a article.

In this research such papers originating from England, Scotland, Northern Ireland, and Wales are grouped under the UK heading, while those from Hong Kong, Macao, and Taiwan are not included under the P.R China heading. The publication indicators for the 20 most productive countries/territories in translational medical research are presented in Table3, which of these 20 productive countries/territories, 12 of which are from Europe, three from Asia, two from North America, one from South America, one from Oceania and none from African countries. Thus it was suggested that economic development and scientific investment has contributed much to the distribution, as some of the major industrialized countries (G7 countries: the USA, the UK, Germany, Canada, Italy, Japan, and France,) and developing countries (P.R China and Brazil) are all among countries within the list. The pattern of domination in publication of the G7 countries has occurred in most scientific fields (Suk et al., 2011), reflecting the high economic activity and academic level of these countries (Arunachalam and Doss, 2000).

In other general medicine such as tropical medicine or health research fields, west Europe, Africa, Latin America, Asia (exclude japan) and the Caribbean are the key production area for these countries or regions need tropical medicine or public health research much to save more person from the edge of death. And in these geographical spaces, the annual publications kept steady as the advanced country such as USA, this is the main different from the translational medicine research in global distribution.

The USA topped first in the productivity ranking of countries, with the highest number of TP. The UK published the second highest ratio of articles, followed by Germany, Canada, Italy, Japan as well as The Netherlands, and the number of publications of other countries is all below 100. Table3 also shows information about the LCS, GCS, and AGCS of research articles for the top 20 countries in the global field of translational medical research. It can be seen that the LCS and GCS of USA is the highest, followed by the UK, Germany, and Canada in turn. The AGCS, sorted in descending order, is Switzerland, Spain, Canada, Italy and the USA. The USA and UK are on the front ranking in AGCS, showing their superiority in translational medical research. Switzerland and Spain rank 11st and 10th in

issued number of articles respectively, and the top two in AVGS, which indicates the high average quality of these articles. Japan ranks 6th in issued volumes while with lower AGCS, which may indicate that there has been a considerable problem with the quality of Japanese articles issued, as is the case with P.R China and France.

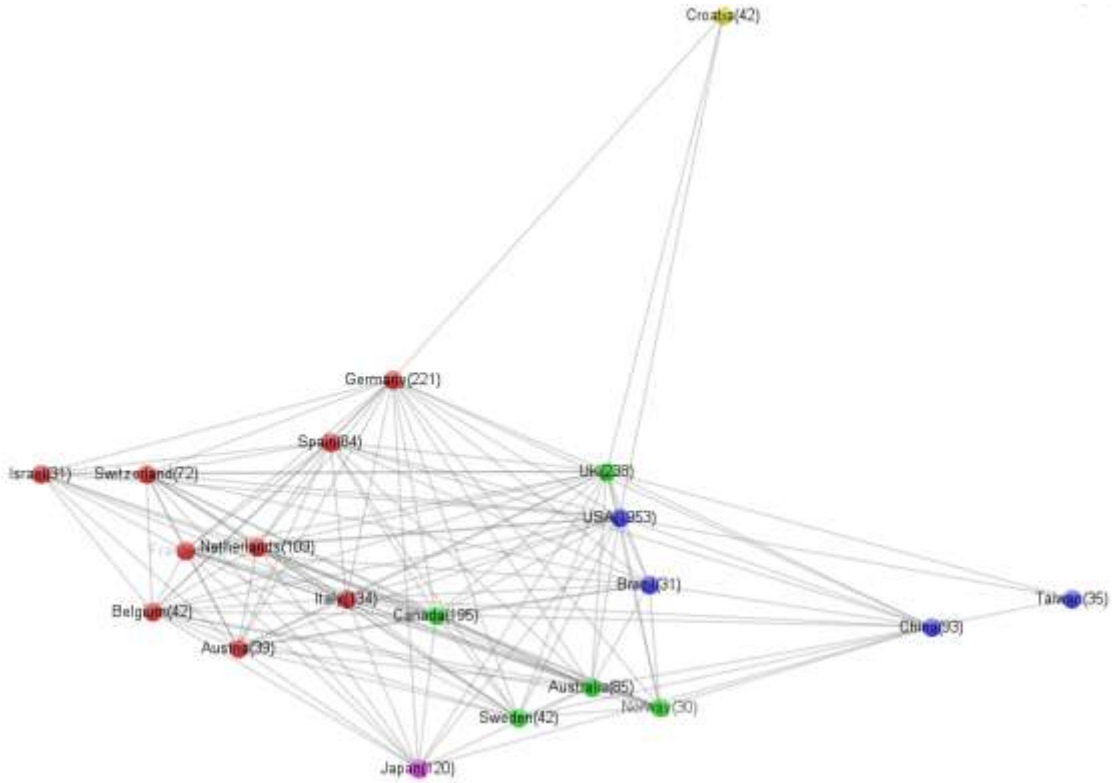

Figure 3. National/Territorial collaboration network of 20 most productive countries (the distance between two circles is inversely proportional to the number of collaboration between nations/territories, i.e., shorter distances suggest more collaboration.)

When analyzing the collaboration patterns for the 20 most productive countries/territories with VOSviewer tool in Figure 3, it was find that several countries/territories tend to cooperate with a small group of collaborators, which have generated five major clusters of countries/territories, each of which usually has several core countries/territories. The USA and UK's central position in translational medical research can be observed by its pivotal role in the national collaboration networks in Figure 3. The eigenvalue centrality not only measures the quantity of research collaborations, but also reveals countries/territories that were pivotal in forming global research communities. The USA and the UK cooperate frequently with other countries/regions and stand in the core position of the entire network, which in turn benefits from their knowledge transfer among translational medical researchers. The other nations, such as P.R China, Taiwan, Brazil and Croatia, are in the peripheral layer. Because these countries/territories have less cooperation with other countries/regions, they are in the outermost layer of the entire cooperation network. As a result, the top two productive countries have carried out most of the international collaborations with others in the translational medical research field.

ℓ **Institutes of publication and collaboration**

Table4. Top 20 most productive Institutions of WoS articles during 1992–2011

No.	Institution	TP	%	LCS	GCS	AGCS
1	University of Michigan	137	4.20	138	1332	9.72
2	Harvard University	116	3.60	34	1332	11.48
3	University of California Los Angeles	80	2.40	124	1053	13.16
4	University of Pittsburgh	75	2.30	16	1402	18.69
5	University California San Francisco	71	2.20	44	635	8.94
6	University of Penney	68	2.10	21	889	13.07
7	NCI	67	2.10	57	959	14.31
8	Univ Minnesota	62	1.90	14	631	10.18
9	Johns Hopkins University	61	1.90	45	814	13.34
10	University of Washington	60	1.80	21	546	9.10
11	Stanford University	55	1.70	7	550	10.00
12	Duke University	54	1.70	24	420	7.78
13	University of Toronto	48	1.50	7	339	7.06
14	Yale University	47	1.40	36	777	16.53
15	Centers of Disease Control & Prevent	46	1.40	139	1228	26.70
16	Indiana University	46	1.40	75	1382	30.04
17	University of Chicago	45	1.40	20	547	12.16
18	Columbia University	43	1.30	16	582	13.53
19	Mayo Clinic	42	1.30	4	234	5.57
20	Kaiser Permanente	41	1.30	108	736	17.95

TP number of articles; %: percentage of articles; LCS, Local Citation Score, is the number of times cited by other papers in the local collection; GCS, Global Citation Score, is the citation frequency based on the full Web of Science count at the time the data was downloaded; AGCS is the average citation frequency of a article.

The contributions of different institutes are assessed herein by the institutes' affiliations with at least one author in the published papers. The top 20 institutes with a paper quantity of more than 40 are ranked by their published articles. According to Table4, University of Michigan and Harvard University perform well, and make up the two of the most powerful institutions in translational medical research. University of Michigan has published 137 articles, ranking first, followed by Harvard University with 116 articles. The GCS of the University of Pittsburgh is the highest, followed by Indiana University, Harvard University and the University of Michigan. Moreover, Indiana University has the highest AVGS, followed by Centers for Disease Control and Prevention. Harvard University is the leading institute in paper quantity, while Indiana University is the leading institute in article quality.

All these institutions are in the United States, with the exception of the University of Toronto in Canada. This reflects the overall strength of North American agencies.

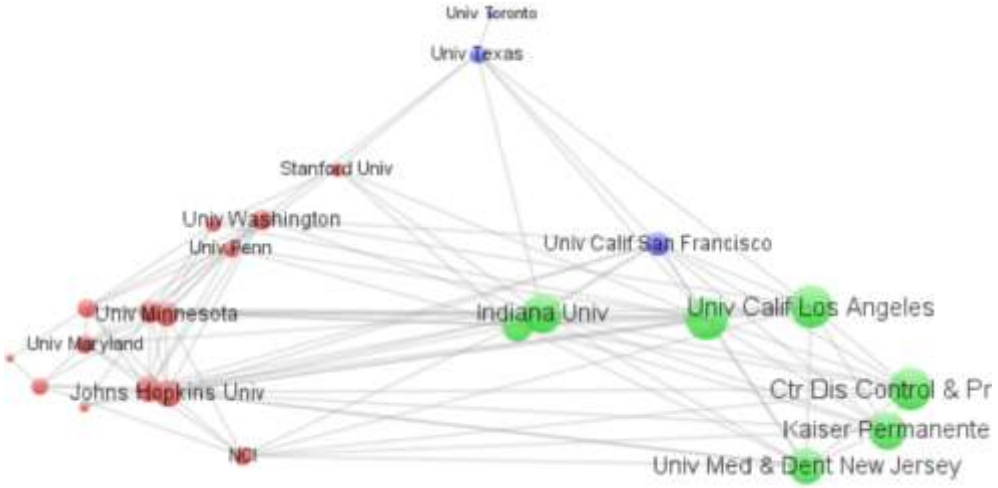

Figure 4. Institutional collaboration network of 25 most central institutions in translational medical research (the size of circles represents the amount of publications, and the distance between two circles is inversely proportional to the number of collaboration between nations/territories, i.e., shorter distances suggest more collaboration.)

As is the case with countries/territories, institutions are central participants in institutional collaboration networks. When analyzing the collaboration patterns of the 25 most productive institutions with VOSviewer tool (Figure 4), it was found that three major clusters of institutions are generated. The American institutes of Harvard University, Johns Hopkins University, University of Michigan, Indiana University, and University of Texas are in the core status of correspondent cluster. These institutions cooperated with other organizations frequently, and thus played an important role in the process of knowledge transfer among organizations. It can be concluded that American institutions have made great advances in paper production and cooperation, with great strengths overall and good development prospects.

In the case of translational medicine research, the distribution of publication and collaboration concentrated in several institutes in advanced country such as USA, while for other general medicine research like tropical medicine or public health, the publication or collaboration is not in concentration as translational medicine distributed. This situation was in same as in the geographical distribution because all the organizations was located in some region or countries.

ℓ MeSH Major Topics and PubMed co-words

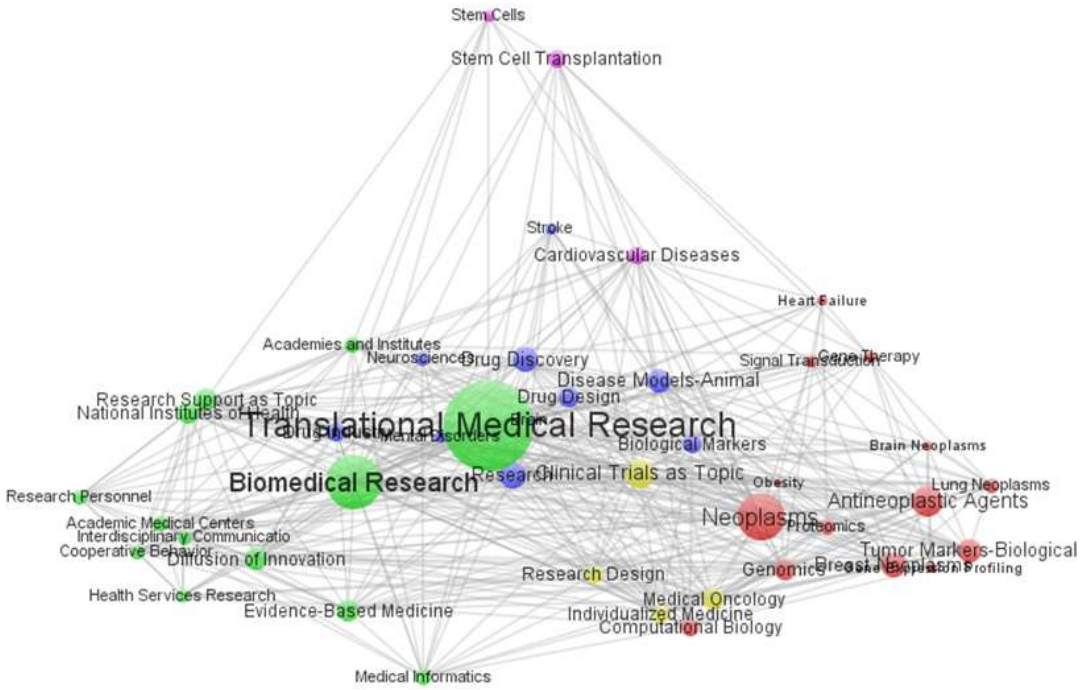

Figure 5. Clusters and co-words map of PubMed papers

The MeSH term, one of the main topics discussed in this articles, is denoted by an asterisk on the MeSH term or MeSH/Subheading combination . Figure 5 shows clusters at the top 45 most-used MeSH terms in the last 20 years. The most frequently used keyword was “Translational Medical Research”, as it was the string used for searching in this study. The total 45 MeSH terms were divided into five groups, and represent the five hot research areas of translational medical research: neoplasms and genomics (e.g. antineoplastic agents, brain neoplasms, breast neoplasms, lung neoplasms, computational biology, gene expression profiling, gene therapy, and genomics); interdisciplinary communication between academic medical centers/institutes (e.g. academic medical centers, academies and institutes, interdisciplinary communication, cooperative behavior, diffusion of innovation, and evidence-based medicine); drug design and development (e.g. disease models-animal, drug design, drug discovery, and drug industry); cardiovascular and brain diseases (e.g. heart failure, and brain and cardiovascular diseases); and biomedical research (e.g. biological markers and computational biology). These five groups are the major hotspots in all translational research topics and thus considered to be the basic academic frontier as Figure 5 shows.

ℓ Co-citation network of references

The co-citation networks based on the documents datasets during 1992-2012 was constructed with CiteSpace with pathfinder network scaling in Figure 6, where Table5 shows detailed information of the critical nodes literature 1 to 11 whose centrality is greater than 0.20.

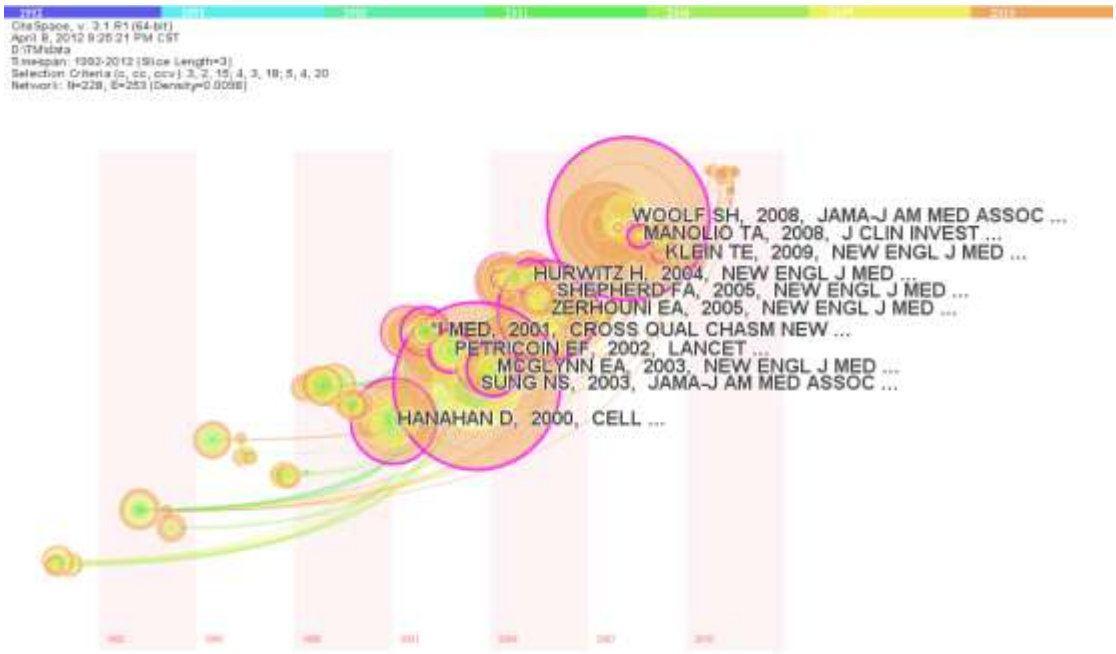

Figure 6. A co-citation network of references cited during 1992–2012 in translational medical research.

Table5. The critical node literature 1 to 11 (arranged by the year)

No	Title	Author	Journal	Year	GS/LCS	Centrality	IF
1	The hallmarks of cancer	Hanahan D, Weinberg RA.	Cell	2000	14737/50	0.20	32.4
2	Crossing the quality chasm: a new health system for the 21st century	Institute of Medicine (IOM)	Book	2001	173/28	0.22	—
3	Use of proteomic patterns in serum to identify ovarian cancer	Petricoin E F, Ardekani A M, Hitt B A, et al	Lancet	2002	3024/24	0.31	38.3
4	The quality of health care delivered to adults in the United States	Mcglynn E A, Asch S M, Adams J, et al	New England Journal of Medicine	2003	3094/30	0.28	53.3
5	Central challenges facing the national clinical research enterprise	Sung N S, Crowley W J, Genel M, et al	JAMA	2003	603/97	0.34	30.0
6	Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer	Hurwitz H, Fehrenbacher L, Novotny W, et al.	New England Journal of Medicine	2004	6030/19	0.20	53.3
7	Translational and clinical science - Time for a new vision	Zerhouni E A	New England Journal of	2005	350/58	0.28	53.3

			Medicine				
8	Erlotinib in previously treated non-small-cell lung cancer	Shepherd F A, Rodrigues P J, Ciuleanu T, et al	New England Journal of Medicine	2005	3262/14	0.23	53.3
9	A HapMap harvest of insights into the genetics of common disease	Manolio T A, Brooks L D, Collins F S	Journal of Clinical Investigation	2008	559/12	0.24	15.4
10	The meaning of translational research and why it matters	Woolf S H	JAMA	2008	508/93	0.21	30.0
11	Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data	Klein T E, Altman R B, Eriksson N, et al	New England Journal of Medicine	2009	510/8	0.27	53.3

The node literature citation frequency was retrieved in both Google Scholar (GS) and Local Citation Sets (LCS) on October 28, 2012; IF (Impact Factor) is from JCR 2011.

Based on their content, the literature 1 to 11 can be divided into two classes: the first class of theory exploration, including the background, intension, meaning, challenges faced, and application prospects of translational medicine; and the second class focused on the knowledge base and specific application fields, such as the diagnosis and treatment of cancer and drug development. The common characteristic of the first group is that their authors or institutions are leading researchers or organizations of medicine in the USA. They mainly explained the background of translational medical research, problems in the American health system, and the meaning, challenges, and future direction of translational medical research from a macro view. They called on researchers worldwide to pay attention to translational research from a strategic height and explored the theories of translational medical research. Specific analysis is as follows:

The first class of critical node literature

The first class of critical node literature includes literature 2, 4, 5, 7 and 10. Their mean citation frequency and centrality is higher than the second class, revealing the theory exploration's core status in the development of translational medicine.

Literature 2 is a report of IOM and RAND Corporation, which pointed out that fundamental changes are needed in the organization and delivery of health care in the United States and that the current health system was unable to meet patients' needs. The healthcare service was confronted with three problems of overuse, underuse, and misuse. The report then presented a health system framework which was safe, effective, patient-centered, timely, efficient, and equitable. This report made an outstanding contribution to thoroughly analyze the problems of the health system of United States and to arise people's thinking of health system. It not only promoted the health reform of United States, but also got off the mark of translational medicine development.

Literature 4 is an extension of the research of literature 2. A random sample of adults living in 12

metropolitan areas in the United States indicated that, on average, Americans received about half of recommended medical care processes (for example, in this study, only 24 percent of participants who had diabetes received three or more glycosylated hemoglobin tests over a two-year period). The study also discovered that deficits in processes involved in primary and secondary preventive care were closely associated with preventable deaths. This work proved the conclusion of literature 2 empirically. Though the article didn't put forward a definite solution to the problem, it indicated that a key component of any solution is the routine availability of information on performance at all levels. It emphasized that establishing a national base line for performance is extremely urgent. The contribution of this article is on the translation of computer science to medicine and the development of health informatization.

Literature 5 has the highest citation frequency and centrality in local citation sets, indicating its crucial role in the development of translational medicine. Breakthroughs in basic biomedical sciences, including human genomics, stem cell biology, biomedical engineering, molecular biology, and immunology, over the past 5 decades have provided an unprecedented supply of information for improving human health, but the scientific discoveries failed to be translated efficiently into tangible human benefit. The article analyzed the two major translational blocks leading to this dilemma: (1) the blocks between the translations from basic science to clinical science; (2) the blocks between the translation from clinical science to clinical practice and health decision making in health system. Then three steps of the solution were put forward: (1)identifying the central challenges facing clinical research—public participation, information systems, workforce training, and funding; (2)making recommendations to the stakeholders for the solution of the problem; (3)inviting a broader, participatory dialogue with a view to improve the overall performance of the US clinical research enterprise. The important contribution of this article is that it emphasized that the translational research is as important as basic research and deserves support; otherwise the discoveries of basic science cannot be translated into the benefit of humans. It laid the foundation for people to understand the importance of translational medicine.

Literature 7 summarized the current condition and magnificent prospect of NIH Roadmap. It introduced the background of NIH Roadmap, and emphasized its strategic goal. The NIH Roadmap included three themes: "New Pathways to Discovery", "Research Teams of the Future" and "Re-engineering the Clinical Research Enterprise". The NIH Roadmap had 28 initial programs and several executing groups that were responsible for the implementation of the programs. It was "a long-term development plan" to the future of life science. The research fields and strategy it identified had guiding significance for future medicine research and it was an important turning point to the development of translational medicine in the United States. From then on, the translational medicine in the US stepped into a fast-growing period (which was in accordance with the analysis of the development period of translational medicine). Further, NIH established the Clinical & Translational Science Awards (CTSA) in 2006 to support the translational research in colleges and universities. With the close collaborations among universities and communities and other stakeholders, many translational centers had been founded by foundations, industry, hospitals and other organizations, which impelled the development of translational medicine in the US and around the world. The establishment of CTSA is a milestone in the history of translational medicine.

Literature 10 is based on the researches above and discussed the meaning of translational medicine and put forward the 2T mode of translational medicine for the first time. T1 has been characterized as follows: "effective translation of the new knowledge, mechanisms, and techniques generated by

advances in basic science research into new approaches for prevention, diagnosis, and treatment of disease is essential for improving health." T2 seeks to close that gap and improve quality by improving access, reorganizing and coordinating systems of care, helping clinicians and patients to change behaviors and make more informed choices, providing reminders and point-of-care decision support tools, and strengthening the patient-clinician relationship. However T2 research evidently lacked attention and funding. The article called on researchers to pay attention to T2 research, because T2 research could save more lives. Starting with T2, more models of translational medicine such as 3T and 4T appeared subsequently, which [the combination of all] marked that translational medicine had stepped into a new stage.

The common characteristic of such five literatures above is that their authors or institutions are leading researchers or organizations of medicine in the US. They mainly explained the background of translational medicine, the problems in the US health system, the meaning, challenges, and future direction of translational medicine in a macro view. They called on researchers worldwide to pay attention to translational research from a strategic height and explored the theories of translational medicine.

The second class of critical node literature

The second class of critical node literature includes literature 1, 3, 6, 8, 9, and 11. This class of literature represents the knowledge base and major application fields of translational medicine. As classic works in specific fields, they are the "test plots" for the application and development of translational medicine.

Literature 1 mainly reviewed the important articles about cancer in the 1990s. Then it discussed the rules that govern the transformation of normal human cells into malignant cancers. The article suggested that the vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. This article revealed a series of symbolic changes in the formation of cancer cells. It provided useful information for researchers who are seeking cancer cell biomarkers, exploring the mechanisms of cancer and developing drugs for cancer treatment. In addition, it laid the basis for scientific discoveries to be translated into cancer diagnosis and treatment.

Literature 3 linked surface-enhanced laser desorption and ionization time-of-flight (SELDI-TOF) mass spectroscopy spectral analysis with a high-order analytical approach using samples from women with a known diagnosis to define an optimum discriminatory proteomic pattern. The discovered pattern was then used to classify an independent set of 116 masked serum samples: 50 from women with ovarian cancer, and 66 from unaffected women or those with non-malignant disorders. The result yielded a sensitivity of 100% (95% CI 93–100), specificity of 95% (87–99). The successful application of this novel approach improved the detection of early-stage ovarian cancer, thus increased the survival rate of ovarian cancer patients. This article led to many researches on the application of research outcomes of proteomics to the detection of early-stage cancers.

Literature 6 selected 813 patients with previously untreated metastatic colorectal cancer, and then randomly assigned 402 to receive irinotecan, bolus fluorouracil, and leucovorin (IFL) plus bevacizumab (5 mg per kilogram of body weight for every two weeks) and 411 to receive IFL plus placebo. The results suggested that the addition of bevacizumab to fluorouracil-based combination chemotherapy resulted in statistically significant and clinically meaningful improvement in survival

among patients with metastatic colorectal cancer. Bevacizumab is a kind of antihuman monoclonal antibody against vascular endothelial growth factor (VEGF) which can inhibit the growth of human tumor vascular. The article proved the feasibility of using VEGF inhibitor to treat cancer, thus opened up a new direction in cancer treatment research.

Literature 8 randomly assigned 731 non–small-cell lung cancer patients in a 2:1 ratio to receive oral erlotinib, at a dose of 150 mg daily, or placebo. The results suggested that erlotinib can prolong survival in patients with non–small-cell lung cancer, which overthrew the research conclusions of Massarelli E et al that third-line chemotherapy was futile for non–small-cell lung cancer patients. It made great contribution to the treatment of non–small-cell lung cancer. Erlotinib is a kind of epidermal growth factor receptor (EGFR) inhibitors, as the overexpression of EGFR was founded in many cancers; this article triggered the following series of research about the application of EGFR inhibitor to the treatment of other cancers.

Literature 9 examined the origin, development, and current status of the HapMap; its prospects for continued evolution; and its current and potential future impact on biomedical science. The International HapMap Project officially started with a meeting on October 27-29, 2002. The goal of the project is to develop a haplotype map of the human genome, the HapMap. Using HapMap as a tool to conduct genome-wide association studies (GWAS), researchers could identify the haplotype including the genes influencing specific diseases. The article named successful GWA studies the most visible and exciting outcome of HapMap to date, with a large number of robust and highly replicated genetic associations with common diseases providing novel and unexpected insights into the pathophysiology of disease. In the long run, however, the greatest contribution of genetic discoveries facilitated by the HapMap may be in the identification of new therapeutic targets, which will cause a revolutionary change of treatments for many diseases.

Literature 11 involved warfarin, which is the most widely used oral anticoagulant agent worldwide. The article used clinical and genetic data from 4043 patients to create a dose algorithm that was based on clinical variables only and an algorithm in which genetic information was added to the clinical variables. Through a validation cohort study of 1009 subjects, they proved that the pharmacogenetic algorithm they developed provided significantly better predictions of the appropriate dose of warfarin than either the clinical algorithm or a fixed-dose approach (especially <21mg or >49mg weekly). The study laid important groundwork for the following prospective trials like it and advanced the application of pharmacogenetic in determining the dose of other drugs.

These six literatures above were all published in journals with highly impact factors and they mainly discussed basic research to clinical practice translation of specific scientific results or diseases in application level. As for the evolution path, the first four articles aim at novel approaches of the diagnosis of cancer and new drugs for the treatment of cancer, involving the fields of cell biology and molecular biology. But after that the next two articles altered the research perspective to explore the genetics of diseases. It indicates that in the beginning, researchers were more concerned about translating the cellular and molecular biology research outcomes to cancer diagnosis and treatment. With the development of genetics, especially with the International HapMap phases I and II data published in 2005 and 2007 respectively, the hot topic of today's translational medicine has gradually turned into the application of basic genetic research data in disease diagnosis, treatment and drug development.

The second class has also focused on the knowledge base and specific application fields, such as the diagnosis and treatment of cancer and drug development. The second class papers are all published in

journals with very high impact factors, where they mainly discuss basic research to clinical practice translation of specific scientific results or diseases in the application level. As for the evolution pathway, the first four articles aim at novel approaches to the diagnosis of cancer and new drugs for the treatment of cancer, involving the fields of cell biology and molecular biology. This indicates that at the beginning, researchers were more concerned about translating the cellular and molecular biology research outcomes into cancer diagnosis and treatment. With the development of genetics, especially with the International HapMap phases I and II data published in 2005 and 2007, respectively, the hot topic of today's translational medical research has gradually become the application of basic genetic research data into disease diagnosis, treatment and even drug development.

ℓ **Distribution of keywords and co-words**

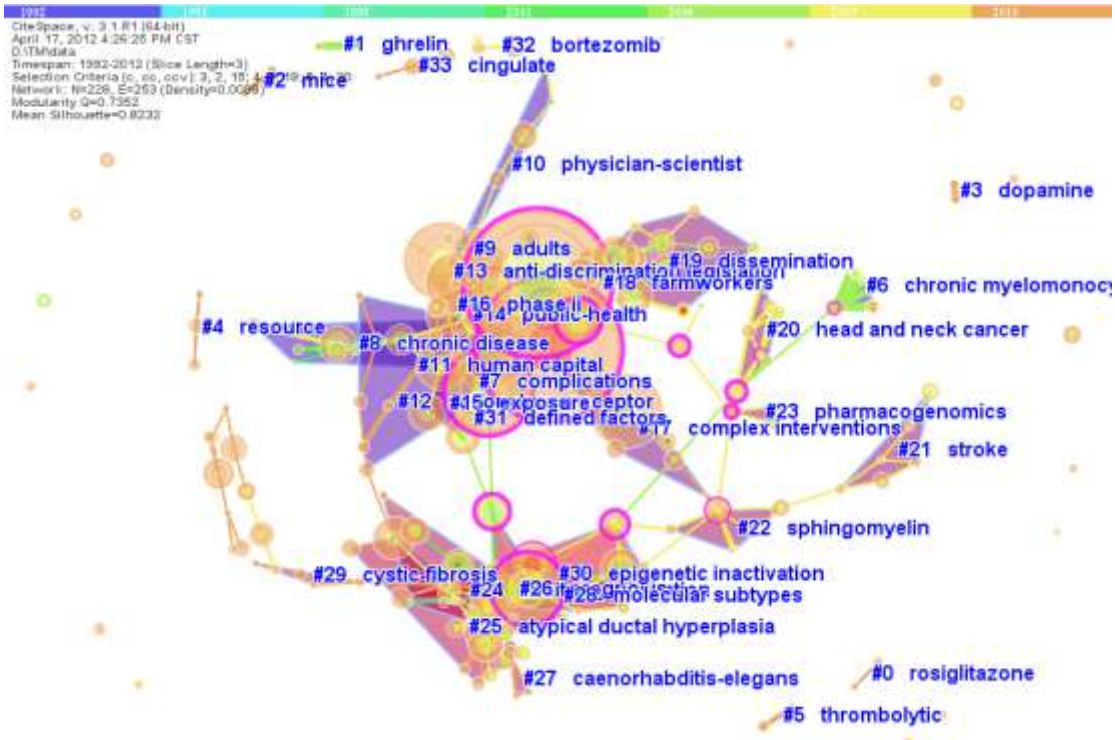

Figure 7. Highly citation literature clustering automatic identification hot topics

Table6. Terms cluster identified with tf * idf weighted values

No.	Scale	S	Mean Time	Top 5 Key Words
31	39	0.31	2004	(14.68) defined factors; (14.45) progenitor cells; (13.99) human somatic-cells; (13.85) bone morphogenetic protein-2; (13.49) stem cell
6	15	1	2000	(20.22) chronic myelomonocytic leukemia; (20.22) factor receptor-beta; (20.22) cell myeloproliferative disorder; (18.79) chronic myelogenous leukemia; (18.4) cytogenetic responses
18	13	0.46	2003	(9.44) farmworkers; (8.71) intervention; (8.49) knowledge translation; (8.42) dissemination; (7.92) workers
24	13	0.87	2000	(12.55) in-situ hybridization; (12.55) gene amplification; (12.46) amplification; (11.11) bladder-cancer; (10.73) oligonucleotide arrays
19	12	0.9	2001	(9.96) dissemination; (9.84) adoption; (9.44) social organizing; (9.44)

				social networks; (9.44) complexity
25	12	0.7	2002	(10.73) atypical ductal hyperplasia; (9.83) subtypes; (9) brca2 mutation; (7.96) molecular subtypes; (7.61) brca1 mutation
8	9	0.76	2001	(12.55) chronic disease; (11.73) maintenance; (10.73) social support; (9.84) complications; (9.84) life-style
30	9	0.8	2004	(7.61) epigenetic inactivation; (7.61) clinical-response; (7) chronic myeloid-leukemia; (6.58) phase-iii trial; (6.39) receptor tyrosine kinase
20	8	0.95	2004	(7.92) head and neck cancer; (7.61) plus cetuximab; (7.2) cetuximab; (7) head; (7) neck
11	7	0.74	2007	(7.61) human capital; (7.61) regulatory science; (7) opinion; (6.58) industry; (6.06) policy
17	7	0.87	2006	(9.44) complex interventions; (9.31) informatics; (8.12) knowledge translation; (7.96) family medicine; (7.93) knowledge
10	6	0.67	2004	(7.87) physician-scientist; (7.19) self-efficacy; (6.33) physician-scientists; (6.33) students; (5.65) attitudes
21	6	0.92	2005	(10.15) stroke; (9.44) oxygen; (9.44) penumbra; (9) embolic stroke; (8.88) neuroprotection
22	6	0.75	2005	(7.61) sphingomyelin; (5.69) metastatic colorectal-cancer; (5.65) rectal-cancer; (5.65) apolipoprotein-e; (5.65) radiation response
28	6	0.65	2004	(7.96) molecular subtypes; (7.96) subtypes; (7.61) gene expression profile; (7.61) hormone-sensitive breast cancer; (7.61) predictive factor

Two groups of clusters are noted in Figure 7, where their mean publishing times are all located after 2000. Retrieving the identified terms in Table2 to refine the original search results, their similar contents are identified as the main research hotspots of the clustering. Specific analysis is as follows:

The group of clusters located in the upper part of Figure 7 is based on the first class of critical node literature, including clusters 18, 19, 8, 11, 17, and 10. Cluster 18 discusses the translation of scientific discoveries into healthcare interventions for underserved populations, such as migrant workers (Garcia et al., 2012). Cluster 19 focuses on the application of complexity science to health system researches (Norman et al., 2010). Cluster 8 explores the ways to reduce chronic disease (such as diabetes) complications morbidity by providing social support and changing life-styles (Porter et al., 2012). Cluster 11 discusses how to improve the efficiency of drug development by management system reform and increasing the cooperation between academic institutions and industry (FitzGerald, 2010). Cluster 17 is mainly concerned with the application of complex interventions to promote community knowledge translation (Rost et al., 2000). Cluster 10 generally addresses the education of physician-scientists and advancing translational research by physician-scientists. As seen from the analysis above, these clusters largely involve clinical epidemiology, communication science, public policy, organizational science, and education, corresponding to T2 research of the translational medical research 2T mode (Rigby, 2010).

The group of clusters located in the lower part in Figure 7 is mainly based on the second class of critical node literature, including clusters 6, 24, 25, 30, 20, 21, 22, and 28. Note that although cluster 31 is in the upper region, it was believed that it should belong to the lower group, considering its identified terms (Lu and Yang, 2011). Cluster 31 mainly involved in the application of stem cells and progenitor cells technologies designed to regenerate vascular, organs, and tissues, thus the treatment of diseases.

This cluster is the largest, for recent advances in material science and stem cell and developmental biology have helped scientists targeted molecules and pathways to help restore the body's regenerative capacity (Runyan and Taylor, 2010). Cluster 6 studies the application of inhibitors of kinases (such as factor receptor-beta) to treat diseases such as chronic myelomonocytic leukemia (Gotlib et al., 2004). Cluster 24 discusses the application of molecular biology techniques such as in-situ hybridization in the diagnosis of breast cancer and bladder cancer (Hoos and Cordon-Cardo, 2001). Cluster 25 is mainly concerned with researches on breast cancer from the perspectives of molecular biology and genetics, with the emphasis on BRCA1 and BRCA2 mutations (Dillon et al., 1998; Lakhani, 2001). Cluster 30 works on receptor tyrosine kinase as the treatment target of cancer (Goetsch and Caussanel, 2010). Cluster 20 focuses on the application of cetuximab (FGER inhibitor) in the treatment of cancer (Psyrri et al., 2010). Cluster 21 is mainly focused on screening stroke patients using magnetic resonance imaging of ischemia penumbra to elevate the success rate of stroke drug clinical trials (Feuerstein and Chavez, 2009). Cluster 22 explores the treatments of Alzheimer's disease (Damani and Topol, 2011; Mielke and Lyketsos, 2010) and cardiovascular disease through studying the function of sphingomyelin and apolipoprotein-E and ways to improve the effect of radiotherapy by discussing the factors influencing radiation response (Debucquoy et al., 2010). Cluster 28 discusses the researches of gene expression profiles to discover new biomarkers as predictors of disease progression in cancer treatment processes so as to assist treatment decisions (Chow, 2010). Compared with the upper cluster group, this cluster group corresponds with the T1 research in the 2T mode of translational medical research. Main hot research areas of diseases include breast cancer, bladder-cancer, colorectal cancer, head and neck cancer, leukemia and other neoplastic diseases, stroke, Alzheimer's disease, among others. Meanwhile the hot substances and methods being used include somatic cells and progenitor cells therapy, stem cell technology, factor receptor-beta, in-situ hybridization, gene amplification technology, BRCA gene mutation, the receptor tyrosine kinase, magnetic resonance imaging methods, (neural) sphingomyelin, apolipoprotein-E, as well as gene expression profiling that involves molecular biology, genetics, and other basic medical research. The application of cetuximab and other drugs has also made progress. The translation of these basic researches has strongly improved the development of new drugs and related diseases diagnosis and treatment technologies.

Conclusions

In this paper, a supplemental evaluation of the status of translational medical research was provided by summarizing document types, languages, publication patterns, subject categories, journals, geographic and institutional distributions, key articles, and the distribution of keywords and Mesh terms. This analysis confirms that papers in translational medical research have increased rapidly during the last 20 years. In total, there are 3,627 research articles in 1,062 journals listed in 91 SCI subject categories. Research on the fields of translational medical research have mainly focused on Research Experimental Medicine, General Internal Medicine, Medical Laboratory Technology, Oncology, Neurosciences Neurology, Cell Biology, Public Environmental Occupational Health, Psychiatry, Health Care Sciences Services, and Pharmacology Pharmacy. All output has been concentrated in several journals such as *Translational Research* (418), *Translational Oncology* (141), *Translational Stroke Research* (110) and *Translational Neuroscience* (107). Most notably, *Translational Research*, supported by the CTSA, has been the chief core journal in the field of translational medical research during last four years.

The translational medical research output is distributed unevenly over all countries. The G7 countries published the large majority of the SCI-E and SSCI articles. The USA contributes more than half of the

total productions and most of the total citation frequencies. In addition, the G7 countries stand in the core position of international collaborative networks and thus promote the creation, transmission and sharing of knowledge in translational medical research fields. Furthermore, American institutions have made great advances in paper production, citation, and cooperation, with great strengths overall and good development prospects. The most frequently cited articles were come from the USA and The Netherlands, during which USA-authored papers contributes the most. It can be concluded that G7 countries make up the leading nations for translational medical research, where the center is the USA.

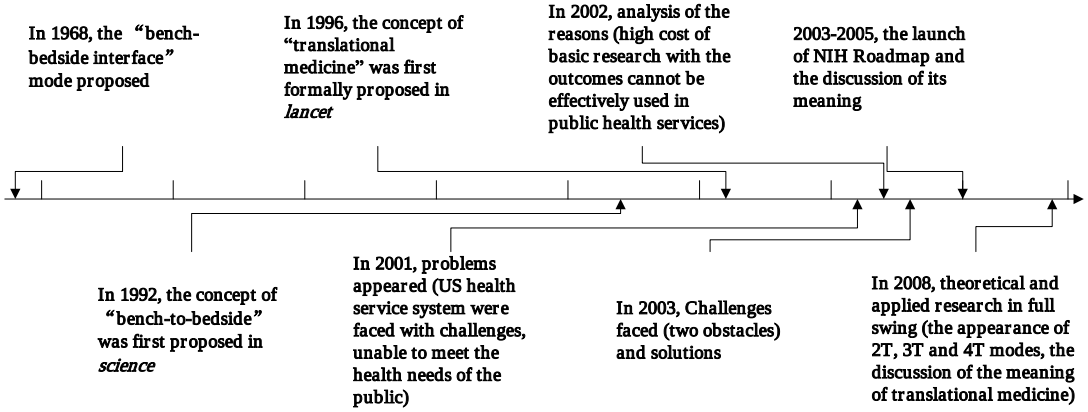

Figure 8. The evolution pathway of translational medical research

The development path and hotspots of translational medical research are systematically studied herein via literature review, citation analysis and the technology of knowledge visualization. The results show a lengthy process (Figure 8) in the developmental stages of translational medical research. From the time the "bench-bedside interface" and "bench to bedside" concepts were proposed to the development of "translational research" and "translational medical research", nearly 30 years have passed. In 21st century, especially after the introduction of the NIH roadmap, translational medical research has come into a phase of rapid development, where its evolution pathway can be summarized as: problems that have appeared (the USA health service system has been faced with challenges in meeting the health needs of the public); cause analysis (the high cost of basic research and their outcomes cannot be effectively used in public health services); challenges faced and solutions proposed (two obstacles of clinical researches in the USA include basic science to clinical science translational obstacles, and clinical research to clinical practice and health care decision-making in health system translational obstacles and solutions); translational medical research programs being formally established (NIH Roadmap for medical research where translational medical research's "long-term development plan" was officially launched); and theoretical and applied research in full swing (the appearance of 2T, 3T, and 4T modes, the discussion of the meaning of translational medical research, and the application of major research achievements of oncology and genetics researches to the treatment of disease and drug development and other aspects). In this process, the outcomes of basic research in the field of oncology and genetics provide a good knowledge base for ascertaining the early development of translational medical research.

At the same time, translational medical researchers have embraced a cross-disciplinary domain of many fields, involving basic medicine, clinical medicine, public health, and life sciences. Its current hotspots center on two fields of public health: health systems research, optimization of management structure, disease control and prevention, health knowledge dissemination and translational medical

research personnel trainings, and so forth; and biomedical research: cancer / breast cancer/ ovarian cancer / bladder cancer / colorectal cancer / head and neck cancer / leukemia / Alzheimer 's disease / stroke / diabetes, genomics / gene expression, proteomics, genetics, stem cells, characterization and application of biomarkers, animal model development, drug development, and so forth. Meanwhile, from the analysis of MeSH terms, the main topics in the translational medical research fields are found to be neoplasms and genomics, interdisciplinary communication between academic medical centers/institutes, drug design and development, cardiovascular and brain diseases, and biomedical research. The research of translation medicine is so different with other general medicine like tropical medicine or public health research in the publication trend or geographical distribution for it was an new emerging research area. However, compared to biomedical research; translational research of public health (T2) needs more attention in the future.

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References

PubMed Help [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK3830/.

Arunachalam, S., and Doss, M.J. (2000). Mapping international collaboration in science in Asia through coauthorship analysis. Curr Sci *79*, 621-628.

Boyack, K.W., Klavans, R., and Borner, K. (2005). Mapping the backbone of science. Scientometrics *64*, 351-374.

Brander, C., Ferrone, S., and Marincola, F.M. (2006). Rewarding patient-directed research: Excellence in Translational Medicine Award. J Transl Med *4*, 19.

Campanario, J.M., Carretero, J., Marangon, V., Molina, A., and Ros, G. (2011). Effect on the journal impact factor of the number and document type of citing records: a wide-scale study. Scientometrics *87*, 75-84.

Chen, K.H., and Guan, J.C. (2011). A bibliometric investigation of research performance in emerging nanobiopharmaceuticals. Journal of Informetrics *5*, 233-247.

Chen, W., Chen, S., Qi, D.C., Gao, X.Y., and Wee, A.T.S. (2007). Surface transfer p-type doping of epitaxial graphene. J Am Chem Soc *129*, 10418-10422.

Chow, L.W. (2010). Gene expression profiles as an additional tool to conventional predictive factors to assist in management of early endocrine responsive breast cancer. Expert Opin Investig Drugs *19 Suppl 1*, S13-17.

Cobo, M.J., Lopez-Herrera, A.G., Herrera-Viedma, E., and Herrera, F. (2011). Science Mapping Software Tools: Review, Analysis, and Cooperative Study Among Tools. J Am Soc Inf Sci Technol *62*, 1382-1402.

Contopoulos-Ioannidis DG, N.E., Ioannidis JP. T (2003). translation of highly promising basic science research into clinical applications. America Journal Medina *114*, 477-484.

CTSAs Advice [Internet]. About CTSAs. Available from: http://www.gloucestershire.police.uk/counterterrorism/CTSAs%20Advice/item3983.html

Damani, S.B., and Topol, E.J. (2011). Emerging clinical applications in cardiovascular pharmacogenomics. Wiley interdisciplinary reviews Systems biology and medicine *3*, 206-215.

Debucquoy, A., Machiels, J.P., McBride, W.H., and Haustermans, K. (2010). Integration of epidermal growth factor receptor inhibitors with preoperative chemoradiation. Clinical cancer research : an official journal of the American Association for Cancer Research *16*, 2709-2714.

Dillon, D.A., Howe, C.L., Bosari, S., and Costa, J. (1998). The molecular biology of breast cancer: accelerating

clinical applications. Crit Rev Oncog *9*, 125-140.

Dougherty, D., and Conway, P.H. (2008). The "3T's" road map to transform US health care: the "how" of high-quality care. JAMA *299*, 2319-2321.

Drolet, B.C., and Lorenzi, N.M. (2011). Translational research: understanding the continuum from bench to bedside. Translational research : the journal of laboratory and clinical medicine *157*, 1-5.

Editor (1968). Phagocytes and the "bench-bedside interface". N Engl J Med *278*, 1014-1016.

Enachescu, C., and Postelnicu, T. (2003). Patterns in journal citation data revealed by exploratory multivariate analysis. Scientometrics *56*, 43-59.

Faba-Perez, C., Guerrero-Bote, V.P., and De Moya-Anegon, F. (2003). Data mining in a closed Web environment. Scientometrics *58*, 623-640.

Feuerstein, G.Z., and Chavez, J. (2009). Translational medicine for stroke drug discovery: the pharmaceutical industry perspective. Stroke *40*, S121-125.

FitzGerald, G.A. (2010). Perestroika in pharma: evolution or revolution in drug development? The Mount Sinai journal of medicine, New York *77*, 327-332.

Freemantle N, C.J., Young P, Mason J, Harrison J (1999). beta Blockade after myocardial infarction: systematic review and metal regression analysis. BMJ *318*, 1730-1737.

Garcia, D., Hopewell, J., Liebman, A.K., and Mountain, K. (2012). The migrant clinicians network: connecting practice to need and patients to care. Journal of agromedicine *17*, 5-14.

Garfield, E. (1990). KeyWords PlusTM: ISIS breakthrough retrieval method. 1. Expanding your searching power on current-contents on diskette. Current Contents *32*, 5-9.

Geraghty, J. (1996). Adenomatous polyposis coli and translational medicine. Lancet *348*, 422.

Goetsch, L., and Caussanel, V. (2010). Selection criteria for c-Met-targeted therapies: emerging evidence for biomarkers. Biomark Med *4*, 149-170.

Gotlib, J., Cools, J., Malone, J.M., 3rd, Schrier, S.L., Gilliland, D.G., and Coutre, S.E. (2004). The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood *103*, 2879-2891.

Hoos, A., and Cordon-Cardo, C. (2001). Tissue microarray profiling of cancer specimens and cell lines: opportunities and limitations. Laboratory investigation; a journal of technical methods and pathology *81*, 1331-1338.

Lakhani, S.R. (2001). Molecular genetics of solid tumours: translating research into clinical practice. What we could do now: breast cancer. Molecular pathology : MP *54*, 281-284.

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

Lou, Y.C., and Lin, H.F. (2012). Estimate of global research trends and performance in family therapy in Social Science Citation Index. Scientometrics *90*, 807-823.

Lu, T.Y., and Yang, L. (2011). Uses of cardiomyocytes generated from induced pluripotent stem cells. Stem cell research & therapy *2*, 44.

Lucio-Arias, D. (2007). A validation study of HistCite (TM): Using the discoveries of fullerenes and nanotubes.

Marincola, F.M. (2003). Translational Medicine: A two-way road. J Transl Med *1*, 1.

McBride P, S.H., Plane MB, Underbakke G, Brown RL (1998). Primary care practice adherence to National Cholesterol Education Program guidelines for patients with coronary heart disease. Arch Intern Med *158*, 1238-1244.

Mielke, M.M., and Lyketsos, C.G. (2010). Alterations of the sphingolipid pathway in Alzheimer's disease: new biomarkers and treatment targets? Neuromolecular Med *12*, 331-340.

Norman, C.D., Charnaw-Burger, J., Yip, A.L., Saad, S., and Lombardo, C. (2010). Designing health innovation networks using complexity science and systems thinking: the CoNEKTR model. J Eval Clin Pract *16*, 1016-1023.

Porter, A., Fischer, M.J., Brooks, D., Bruce, M., Charleston, J., Cleveland, W.H., Dowie, D., Faulkner, M., Gassman, J., Greene, T.*, et al.* (2012). Quality of life and psychosocial factors in African Americans with hypertensive chronic kidney disease. Translational research : the journal of laboratory and clinical medicine *159*, 4-11.

Pouris, A., and Pouris, A. (2011). Scientometrics of a pandemic: HIV/AIDS research in South Africa and the World. Scientometrics *86*, 541-552.

Psyrri, A., Licitra, L., Lacombe, D., Schuuring, E., Budach, W., Ozsahin, M., Knecht, R., Vermorken, J.B., and Langendijk, J.A. (2010). Strategies to promote translational research within the European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group: a report from the Translational Research Subcommittee. Ann Oncol *21*, 1952-1960.

Rigby, M.R. (2010). The role of the physician-scientist in bridging basic and clinical research in type 1 diabetes. Current opinion in endocrinology, diabetes, and obesity *17*, 131-142.

Rost, K., Nutting, P.A., Smith, J., and Werner, J.J. (2000). Designing and implementing a primary care intervention trial to improve the quality and outcome of care for major depression. General hospital psychiatry *22*, 66-77.

Rubio, D.M., Schoenbaum, E.E., Lee, L.S., Schteingart, D.E., Marantz, P.R., Anderson, K.E., Platt, L.D., Baez, A., and Esposito, K. (2010). Defining translational research: implications for training. Acad Med *85*, 470-475.

Runyan, C.M., and Taylor, J.A. (2010). Clinical applications of stem cells in craniofacial surgery. Facial plastic surgery : FPS *26*, 385-395.

Suk, F.M., Lien, G.S., Yu, T.C., and Ho, Y.S. (2011). Global trends in Helicobacter pylori research from 1991 to 2008 analyzed with the Science Citation Index Expanded. Eur J Gastroenterol Hepatol *23*, 295-301.

van Eck, N.J., and Waltman, L. (2010). Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics *84*, 523-538.

Wang, C.D., and Wang, Z. (1998). Evaluation of the models for Bradford's law. Scientometrics *42*, 89-95.

Wang, L., and Pan, Y.-t. (2010). Research frontiers and trends in graphene research. New Carbon Mater *25*, 401-408.

Westfall, J.M., Mold, J., and Fagnan, L. (2007). Practice-based research--"Blue Highways" on the NIH roadmap. JAMA *297*, 403-406.

Woolf, S.H. (2008). The meaning of translational research and why it matters. JAMA *299*, 211-213.

Zerhouni, E.A. (2005). Translational and clinical science--time for a new vision. N Engl J Med *353*, 1621-1623.