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Global liposome research in the period of 1995–2014: a bibliometric analysis

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Abstract In this study, we aim to evaluate the global scientific output of liposome research, and try to find an approach to quantitatively and qualitatively assess the current global research on liposome. Data were based on the science citation index expanded database, from the Institute of Scientific Information Web of Science database. Bibliometric method was used to analyze publication outputs, journals, countries/territories, institutions, authors, research areas, research hotspots and trends. Globally, there were 37,327 publications referring to liposome during 1995–2014. Liposome research experienced notable growth in the past two decades. The International Journal of Pharmaceutics published the largest number of liposome-related publications in the surveyed period. Major author clusters and research regions are located in the USA, Western Europe, and Asia. The USA was a leading contributor to liposome research with the largest number of publications. The Osaka Univ (Japan), Kyoto Univ (Japan), and Univ Texas (USA) were the three institutions with the largest number of liposome-related publications. Van Rooijen N (Netherlands) was a leading contributor to liposome research with the largest number of publications. The chemistry accounts for the largest number of publications in the research area of liposomes. A keywords analysis revealed that gene, drug delivery, cell and cancer were the research hotspots in the study period. The nanotechnology, drug delivery, small interfering RNA and cancer therapy received dramatically increased attention during the analyzed period, possibly signaling future research trends. Bibliometric method could quantitatively characterize the development of global liposome research.

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Keywords Liposome · Bibliometric analysis · SCIE database · Research hotspot · Research trend

Introduction

Liposomes were first described by British haematologist Alec D Bangham in 1961 (published 1964), at the Babraham Institute, in Cambridge (Kundu et al. 2014). From their studies, it was recognized that phospholipids in aqueous systems are made up of closed bilayer structures (Bangham et al. 1962; Horne et al. 1963; Bangham and Horne 1964). Liposomes can be classified according to their lamellarity, where unilamellar vesicles comprise one lipid bilayer and contain large aqueous internal phase, and multilamellar vesicles consist of several concentric lipid bilayer with micron size. Liposomes form spontaneously when certain lipids are hydrated in aqueous media. Biocompatibility of lipids broadens the applications of liposomes. The combination of the vast knowledge of lipids and their biophysical and biochemical properties with nanotechnology, anatomy, biochemistry, physiology, medicine, pharmacology, and pharmacy, has been translated into the development of this new class of therapeutic modalities benefitting many people around the globe (Caracciolo 2015). Researches on liposome have been published in a large number of journals from authors distributed all over the world. However, there have been few attempts at gathering systematic data on the global scientific production of liposome research. Therefore, there is a need for innovative studies to make sense of the subsequent ballooning number of publications in the area.

In recent years, bibliometrics has been widely applied in various fields to identify productivity of authors, institutions and countries/territories, evaluate geographic distributions and international collaborations, and study research hotspots and trends in specific fields (Pritchard 1969; Chen et al. 2012; Yang et al. 2013; Lu et al. 2014; Yang et al. 2014; Wang et al. 2014; Armfield et al. 2014; Chen et al. 2014).

In this study, bibliometric approaches were used to quantitatively and qualitatively investigate global liposome research during 1995–2014. Specifically, this article aims at identifying general patterns for publication outputs and journals in liposome research, evaluating national, institutional and author research, and summarizing global research areas, research hot issues and trends.

Materials and methods

The data for this paper were collected from the online version of SCIE database of the Web of Science from Thomson Reuters on 6th October 2014. The SCIE database is a leading and frequently used metric of scientific accomplishment in most fields of human creativity (Li et al. 2009).

"Liposome*" was used as the keyword to search titles, abstracts, and keywords from 1995 to 2014. The term listed above could help retrieve the vast majority of liposome-related publications. Although there may be other less common liposome-related terminology, they account for a small number of publications and may have marginal relation to liposome research. The analyses about different document categories including publication outputs, journals, countries/territories, institutes, authors and keywords are presented as follows.

Contributions of different countries and institutions were estimated by the affiliation of at least one author to the publications. The collaboration with different countries was estimated by the location of the affiliation of at least one author of the published papers.

Publications reported from England, Northern Ireland, Scotland, and Wales were included under the UK heading (Zhuang et al. 2012). Publications from Hong Kong have been included with the publications from mainland China under the denomination the People's Republic of China (Canas-Guerrero et al. 2013).

The impact factor of a journal was determined for each document as reported in the Journal Citation Reports Science Edition 2013, which was the latest version available when we planned this study (http://admin-apps.webofknowledge.com/JCR/JCR?RQ=HOME, accessed on April 3, 2015) (Huang 2009).

The economic data were obtained from the website of the World Bank (http://data.worldbank.org/country, accessed on March 29, 2015).

ArcGIS, CiteSpace, science of science (Sci^2), and VOSviewer were employed to analyze the publications for knowledge mapping (Cobo et al. 2011).

Results and discussion

Characteristics of publication outputs

From this study, 13 document types were found in the total 37,327 publications during the 20-year study period. In addition, among the various document types (Publications, letters, software reviews, book reviews, etc.), articles (29,488) constituted the majority (79 %) of documents used in this survey (Fig. 1).

Analyzing the languages used in the investigation, English stands out at 98.41 %, which indicates the relevance of English in the scientific field. Other languages are barely present in this field of investigation, with none reaching in any case even 1 %. This shows the extraordinary relevance of English in this field.

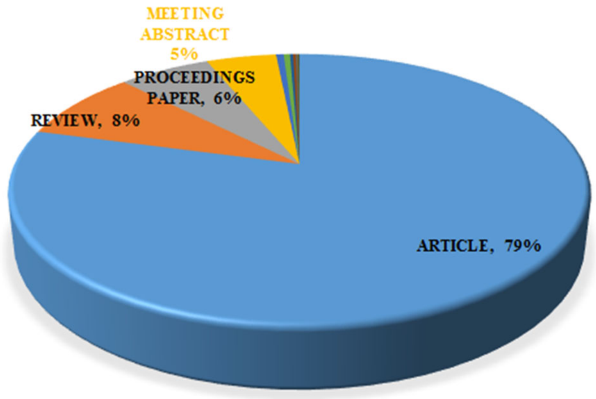

Fig. 1 Categorization of liposome research publications by document type, 1995–2014

From 1995 to 2014, the number of publications increases, followed by a decline in 2014 (shown in Fig. 2a), which can be attributed to an uncompleted statistical analysis in the latest year. Linear model is established to describe the relationships between the annual cumulative number of publications and the publication year (shown in Fig. 2b). A correlation between the annual cumulative number of publications and the publication year is observed, with high coefficients of determination ($R^2 = 0.9928$). The linear fitting results are $y = 1868.3x - 4e{+}06$, where y is the annual cumulative number of publications, and x is the years since 1995. The model predicts an increase in the number of future publications compared with those in 2014, based on the assumption that the growth rate maintained at the level of 1995–2014.

To obtain an overview of liposome research, the annual number of publications during 1995–2014 was displayed in Table 1. The number of liposome publications increased from 1468 in 1995 to 1815 in 6th October 2014, with the total publications reaching 37,327. The

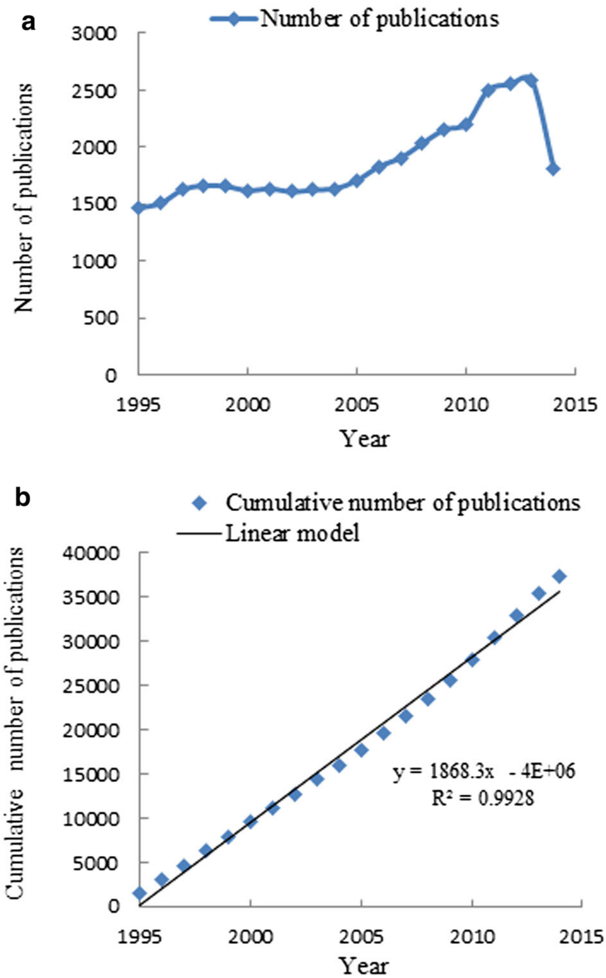

Fig. 2 Trends of **a** number of publications and **b** cumulative number of publications from 1995 to 2014

Table 1 Characteristics of publication outputs from 1995 to 2014

PY	TP	AU	AU/TP	PG	PG/TP	NR	NR/TP	TC	TC/TP
1995	1468	6086	4	11,604	7.9	48,761	33	57,508	39
1996	1506	6289	4	11,296	7.5	46,671	31	54,699	36
1997	1625	7181	4	12,738	7.8	53,300	33	54,858	34
1998	1663	7390	4	13,643	8.2	56,842	34	58,661	35
1999	1655	7433	5	13,906	8.4	57,621	35	59,121	36
2000	1619	7575	5	13,997	8.6	58,809	36	61,996	38
2001	1635	7470	5	14,688	9.0	65,334	40	64,875	40
2002	1608	7287	5	13,545	8.4	59,940	37	55,447	35
2003	1625	7334	5	14,286	8.8	59,780	37	53,397	33
2004	1635	8030	5	14,021	8.6	59,386	37	53,221	33
2005	1708	8363	5	14,762	8.6	63,638	37	55,632	33
2006	1829	9189	5	15,341	8.4	72,075	39	53,413	29
2007	1906	9695	5	15,742	8.3	73,629	39	47,102	25
2008	2035	10,706	5	17,517	8.6	85,213	42	46,704	23
2009	2154	11,423	5	18,643	8.7	94,103	44	42,144	20
2010	2205	12,475	6	19,035	8.6	95,184	43	33,339	15
2011	2500	11,442	5	17,370	6.9	87,817	35	20,244	8
2012	2552	14,286	6	23,147	9.1	120,302	47	17,303	7
2013	2584	17,777	7	28,688	11.1	147,706	57	8337	3
2014	1815	10,659	6	17,489	9.6	91,701	51	698	0
Average			5		8.6		39		26

PY published year, *TP* total publications, *AU* author number, *AU/TP* author number per publication, *PG* page count, *PG/TP* page count per publication, *NR* cited reference count, *NR/TP* cited reference count per publication, *TC* number of citations, *TC/TP* number of citations per publication

number of publications per year has increased steadily since approximately 2003. And the average publication lengths fluctuated slightly, with an overall average of 8.6 pages. 33 references were cited per publication in 1995, comparing to 51 references per publication in 2014, with slight increases throughout the 20 years. The number of authors carrying out research on liposome increased from 6086 in 1995 to 10,659 in 6th October 2014, the average number of authors of a single publication was 5. The average number of citations per publication declined, with an overall average of 26, because older publications inherently had a higher number of citations.

Journal analysis

Overall, 2133 different academic journals have published scholarly publications related to liposome, and the 20 most active journals are presented in Table 2. The 20 most active journals (0.94 % journals) account for 9681 or 25.9 % of the 37,327 publications in the totality. The International Journal of Pharmaceutics published the largest number of liposome-related publications. Furthermore, the ratio of the number of liposome-related publications in a journal (TPJ) to the total number of publications in the journal (TJP) during 1995–2014 (TPJ/TJP) was also calculated and shown in Table 2. The Journal of Liposome Research (TPJ/TJP = 75.9 %) devoted substantial emphasis to liposome studies.

Table 2 The 20 most active journals in liposome research

Journal	Country	TPJ (%)	TJP	TPJ/TJP (%)	IF2013
International Journal of Pharmaceutics	Netherlands	1068 (2.9)	10,253	10.4	3.785
Journal of Controlled Release	Netherlands	925 (2.5)	6535	14.2	7.261
Biochimica et Biophysica Acta-Biomembranes	Netherlands	911 (2.4)	5252	17.4	3.431
Langmuir	USA	774 (2.1)	32,689	2.4	4.384
Journal of Biological Chemistry	USA	573 (1.5)	96,562	0.6	4.6
Biophysical Journal	USA	561 (1.5)	65,002	0.9	3.832
Journal of Liposome Research	USA	525 (1.4)	692	75.9	1.533
Biochemistry	USA	428 (1.2)	32,036	1.3	3.194
Pharmaceutical Research	Germany	405 (1.1)	5494	7.4	3.952
Colloids and Surfaces B-Biointerfaces	Netherlands	398 (1.1)	5270	7.6	4.287
Journal of Drug Targeting	UK	378 (1.0)	1361	27.8	2.723
Biomaterials	Netherlands	373 (1.0)	11,774	3.2	8.312
Journal of Pharmaceutical Sciences	USA	331 (0.9)	6092	5.4	3.007
Chemistry and Physics of Lipids	Netherlands	325 (0.9)	3001	10.8	2.593
Bioconjugate Chemistry	USA	294 (0.8)	3936	7.5	4.821
Advanced Drug Delivery Reviews	Netherlands	293 (0.8)	2459	11.9	12.707
Biochemical and Biophysical Research Communications	USA	292 (0.8)	39,643	0.7	2.281
Proceedings of the National Academy of Sciences of the United States of America	USA	285 (0.8)	68,004	0.4	9.809
Journal of Physical Chemistry B	USA	273 (0.7)	36,084	0.8	3.377
Gene Therapy	UK	269 (0.7)	4073	6.6	4.196

TPJ (%) total number of liposome-related publications in a journal (followed by the percentage of liposome-related publications in the journal of the total liposome-related publications), *TJP* total number of publications in a journal, *TPJ/TJP (%)* the percentage of liposome-related publications in the journal of the total publications in the journal, *IF 2013* impact factor of the journal in 2013

Among the 20 most active journals that covered liposome research, Advanced Drug Delivery Reviews had an impact factor >10.0, though it ranked lower in terms of the total number of publications (López-Muñoz et al. 2014). Journals that had impact factors ranging from 4.0 to 10.0 accounted for 11.3 % of the publications, and 14.8 % of the papers were published in journals with an impact factor between 1.0 and 4.0. The USA has a top ranking with ten journals. It is followed by Netherlands with seven journals.

Country/territory, institution and author analysis

Country/territory analysis

Overall, 100 different countries/territories have published scholarly publications related to liposome. Table 3 lists the 20 most active countries/territories with the total number of liposome-related publications (TPC), sum of the times cited (STC), citing publications (CP), average citations per item (ACI), h-index, gross domestic product (GDP),

Table 3 The 20 most active countries/territories in liposome-related research

Countries/ Territories	TPC (%)	STC	CP	ACI	h-index	GDP (billion, $)	TP (million)	GPC ($)	PPC
USA	10,914 (29.2)	304,500	175,635	35.3	199	16,770	316.1	53,470	34.5
Japan	4983 (13.4)	91,202	59,519	21.6	106	4920	127.3	46,330	39.1
China	3514 (9.4)	26,931	20,129	10.0	59	9240	1357.0	6560	2.6
Germany	2768 (7.4)	66,670	52,531	27.9	101	3730	80.62	47,270	34.3
France	2128 (5.7)	50,325	38,242	27.5	92	2806	66.03	43,460	32.2
UK	1963 (5.3)	34,372	26,016	21.5	77	2678	64.1	41,680	30.6
Italy	1854 (5.0)	43,404	30,208	29.3	88	2149	59.83	35,860	31.0
Canada	1773 (4.8)	42,334	33,656	32.0	91	1827	35.16	52,200	50.4
Netherlands	1489 (4.0)	40,163	30,157	32.2	88	853.5	16.80	51,060	88.6
India	1399 (3.7)	15,373	11,021	13.3	54	1877	1252.0	1570	1.1
Spain	1220 (3.3)	19,030	14,342	17.7	58	1393	46.65	29,920	26.2
South Korea	1014 (2.7)	16,692	13,514	18.0	57	1305	50.22	25,920	20.2
Switzerland	788 (2.1)	23,495	18,478	34.8	71	685.4	8.081	90,760	97.5
Russia	752 (2.0)	8010	6577	12.2	44	2097	143.5	13,850	5.2
Brazil	658 (1.8)	8539	6688	14.3	42	2246	200.4	11,690	3.3
Israel	649 (1.7)	15,258	15,258	27.7	61	290.6	8.059	33,930	80.5
Sweden	615 (1.6)	19,036	13,981	36.5	72	579.7	9.593	61,760	64.1
Poland	561 (1.5)	6760	5470	13.1	32	525.9	38.53	13,240	14.6
Australia	544 (1.5)	11,943	10,515	27.4	51	1560	23.13	65,390	23.5
Denmark	481 (1.3)	9139	7251	22.7	48	335.9	5.614	61,680	85.7

TPC total number of liposome-related publications in an country/territory (followed by the percentage of liposome-related publications in the country/territory of the total liposome-related publications), *STC* sum of the times cited, *CP* citing publications, *ACI* average citations per item, *h-index* defined by the number h of papers among a country/territory's number of publications (Np) that have at least h citations each, *GDP* gross domestic product (2013), *TP* total population (2013), *GPC* gross national income per capita (2013), *PPC* publications per million capita

total population (TP), gross national income per capita (GPC), and publications per million capita (PPC). The USA accounts for the largest number of publications, which includes the number of sum of the times cited, citing publications, average citations per item, and h-index. Japan comes second, followed by China, Germany, and France. The ACI indicates the average impact of the publications of a country, and the h-index (defined as the number h of papers among a country/territory's number of publications (Np) that have a least h citations each) is used to find which country has the largest number of high-quality publications in the liposome field. It is seen in Table 3 that liposome-related publications authored in Sweden have the highest average impact (ACI, 36.5). Although the USA (ACI, 35.3) ranked 2nd in the ACI index, it has the largest number of high-quality (199 publications with more than 199 citations each) in the liposome field.

Eight countries (USA, Japan, China, Germany, France, UK, Italy and Canada) with the top 11 highest country GDP also ranked as the top 8 most productive countries which published papers related to liposome research. Domination in publication is not surprising from mainstream countries since this pattern has occurred in most scientific fields. To a certain extent, large numbers of research publications from a country are correlated with the high economic level of the country. The USA with the highest GDP, showed the greatest counts of publications in liposome, and was followed distantly by other countries.

We calculated the proportion of publications that was attributed to high income, upper middle-income, lower middle-income, and low-income countries, as categorized by the World Bank (Mars et al. 2015). This categorization is according to 2013 Gross National Income per capita (GPC). In our data set from the 20 most active countries/territories, 17 high-income countries published 34,496 papers (Table 2), and the other three middle-income countries (China, India and Brazil) published 5571 papers.

When the ranking of the 20 most productive countries on liposome research was analyzed using indicators such as TP and PPC, populous and developing countries (China, India, Brazil) ranked lower than underpopulated and developed countries (Switzerland, Netherlands, Denmark, Israel, Sweden, Canada, Japan, Germany, France, Italy, UK, Spain, Australia, South Korea, Poland, Russia). Although USA has a large population of about more than 300 million persons, the PPC of USA remained one of the most numbers per million persons (34.5, 8th).

ArcGIS was used to visualize and analyze the worldwide distribution of publications in liposome. Affiliations of authors were mapped worldwide using red dots as shown on Fig. 3. The number of publications in liposome by country/territory was color mapped in Fig. 3, also. It is seen that author clusters and major research regions are mainly located in the USA, Western Europe, and Asia. The cluster of Western Europe gravitates mainly towards Germany, France, UK and Italy. Japan, Eastern China and India were the major areas for liposome-related publications in Asia. These clusters of authors were consistent with the fact that these regions are developed economies and house a large number of academic institutions.

Internationally-coauthored publications on liposome abound during 1995–2014. The research cooperation between countries can be seen from Fig. 3. The USA mainly cooperates with Western Europe, Eastern China and Japan; Western Europe mainly cooperates

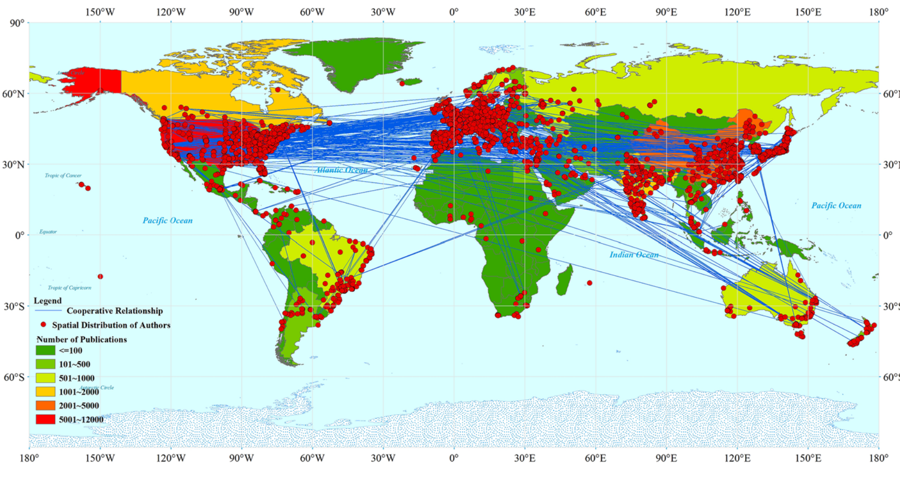

Fig. 3 Global geographic distributions of authors according to the total number of publications by country/territory

with the USA, Eastern China and Eastern Australia; Japan mainly cooperates with the USA and Western Europe; China mainly cooperates with the USA and Western Europe; Eastern Australia mainly cooperates with Western Europe, the USA and Korea; Brazil mainly cooperates with the USA, Western Europe and India. The collaboration on countries seems to indicate a greater globalization and structuration of the research carried out, with more complex and articulated research networks present. It indicated that research in liposomes had become more globally connected. The increased case of communication in a technologically connected world contributed to the increasing collaboration. It would be reasonable to assume that more international collaboration would lead to more output due to the sharing of ideas and workloads.

Institution analysis

CiteSpace was used to visualize the distribution of institutes (Fig. 4). It should be noted that the frequency analysis was based on a total of 4549 institutes. It is noted here that the concentric circles of different colors represent publications in various time slices and the diameter of the circle thus represents the frequency of the institute. Obviously, the important research institutes are mainly originated from the USA and Japan. Table 4 gives top ten institutes in terms of frequency. Osaka Univ has a top ranking. It is followed by Kyoto Univ. Institutes are mainly from the USA and Japan, as mentioned above. The USA accounts for the largest number of institutes. Apart from that, there are still other institutes participating in the research of liposome, such as Univ Utrecht (Netherlands), CNRS (France), Univ British Columbia (UK), and CSIC (Spain). Thus, major universities and research centers have played an important role in the research activities of liposome.

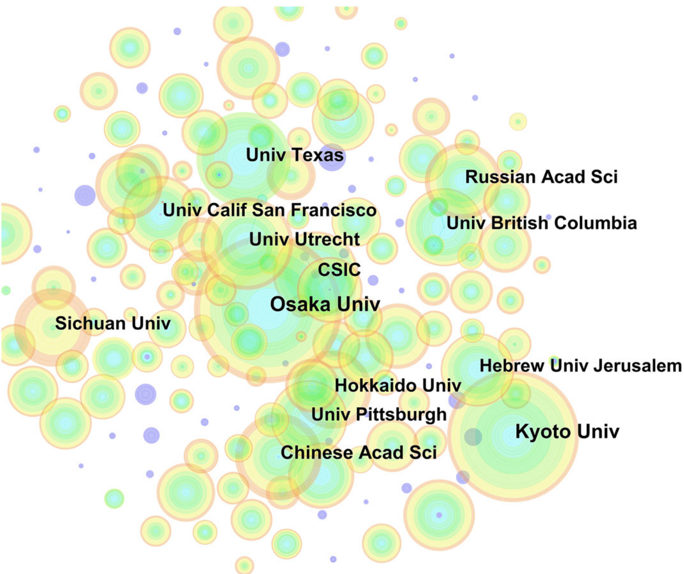

Fig. 4 Institutes with respect to frequency (numbers of publications)

Table 4 Top 10 institutes based on frequency (numbers of publications)

Institute (country)	Frequency
Osaka Univ (Japan)	599
Kyoto Univ (Japan)	521
Univ Texas (USA)	400
Univ Utrecht (Netherlands)	383
Univ Pittsburgh (USA)	345
Univ Calif San Francisco (USA)	345
Harvard Univ (USA)	344
CNRS (France)	317
Univ British Columbia (UK)	316
CSIC (Spain)	308

Author analysis

Overall, 28,300 authors have published scholarly publications related to liposome. Table 5 gives top 20 authors in terms of frequency (numbers of publications). Van Rooijen N (Netherlands) has a top ranking. Japan accounts for the largest number of authors with the most publications (10; or 50.0 % of the total), China (3) comes second, followed by the USA (2) and Netherlands (2).

We used Sci^2 to illustrate the collaboration of authors with the most papers (Fig. 5). Author nodes are color and size coded by the number of publications per author. Edges are color and thickness coded by the number of times two authors wrote a paper together. The remaining commands identify the top-22 authors with the most publications and make their name labels visible.

Clearly, Van Rooijen N (Netherlands) with the most published papers, cooperates with Storm G (Netherlands) and Maruyama K (Japan); Kaneda Y (Japan), Morishita R (Japan) and Ogihara T (Japan) have many cooperations, and they are mainly from Osaka Univ; Storm G (Netherlands) mainly cooperates with Crommelin Dja (Netherlands); Huang L (USA) is also an important author in the field; Harashima H (Japan), Kiwada H (Japan) and Ishida T (Japan) have many cooperations, and they are mainly from Tokushima Univ; Hashida M (Japan), Yamashita F (Japan) and Kawakami S (Japan) have many cooperations, and they are mainly from Kyoto Univ.

Table 5 Top 20 authors based on frequency (numbers of publications)

Author (country)	Frequency	Author (country)	Frequency
Van Rooijen N (Netherlands)	250	Parra JI (Spain)	128
Kaneda Y (Japan)	242	Zhang Y (China)	116
Storm G (Netherlands)	241	Oku N (Japan)	111
Huang L (USA)	197	Liu Y (China)	111
Harashima H (Japan)	171	Zhang L (China)	109
Torchilin Vp (USA)	167	Ishida T (Japan)	109
Hashida M (Japan)	152	Morishita R (Japan)	108
Maruyama K (Japan)	133	Kawakami S (Japan)	104
Kiwada H (Japan)	130	Sakai H (Japan)	103
Barenholz Y (Israel)	129	Vyas Sp (India)	102

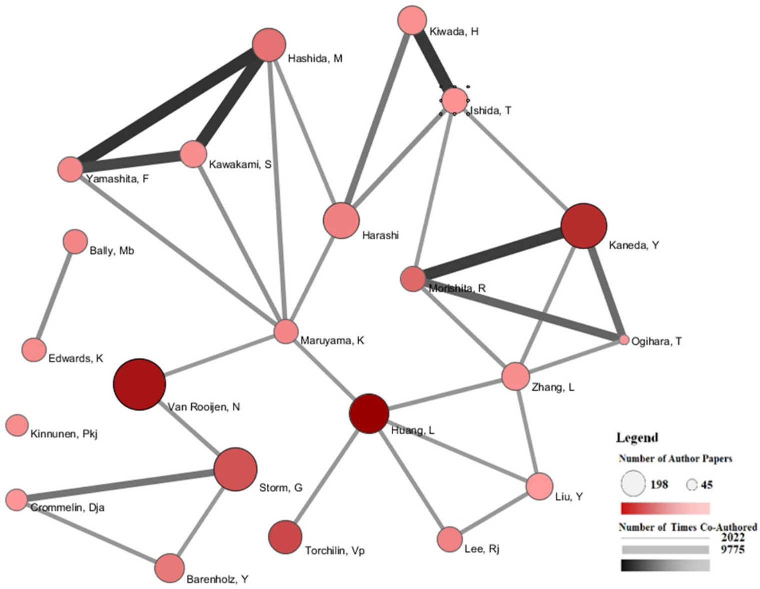

Fig. 5 Collaboration of authors with the most publications

Research areas

A wide variety of research areas are related to liposome research. Overall, there're 106 research areas in the aspect of liposome. Table 6 shows the top 20 most frequently appeared research areas in publications of liposome field during 1995–2014. The chemistry accounts for the largest number of publications. Biochemistry molecular biology comes second, followed by pharmacology pharmacy, biophysics, materials science, and research

Table 6 The 20 most frequently appeared research areas for the study period

Area	Frequency	Area	Frequency
Chemistry	9645	Immunology	1352
Biochemistry molecular biology	9098	Physics	1285
Pharmacology pharmacy	8997	Genetics heredity	951
Biophysics	4099	Polymer science	880
Materials science	3268	Food science technology	779
Research experimental medicine	2217	Radiology nuclear medicine medical imaging	686
Biotechnology applied microbiology	2070	Microbiology	580
Oncology	2020	Cardiovascular system cardiology	539
Cell biology	1901	Neurosciences neurology	493
Engineering	1581	Hematology	481

experimental medicine. Therefore, liposome research is multi-facets and cover a quite wide range of interests, from drug delivery, to biochemistry, to biophysics, to materials science, to biotechnology, to engineering, and also recently, to chemistry.

Research hotspots and trends

Keywords provide a reasonable description of a publication's theme, and could reveal the profile of an author's research preferences (Sun et al. 2012). Therefore, keyword analysis can be used to identify the subjective focus and emphasis specified by authors, explore research hotspots, and discover scientific research trends (Xie et al. 2008). To obtain accurate results, we preprocessed the keywords by merging the singular and plural forms of the same terminology, and those keywords with the same meaning while using different expressions (for example, "liposome" and "liposomal").

Research hotspots

There're 20,282 keywords in the aspect of liposome. Table 7 shows the top 20 most frequently used keywords appeared in publications of liposome field during 1995–2014. With the exception of "liposome", which is the search word in this study, the four most frequently used keywords were "gene", "drug delivery", "cell" and "cancer". Obviously, topics of gene, drug delivery, cell and cancer attracted the greatest attention in liposome-related research.

The visualization, known as foam tree, was generated using Carrot, http://search.carrotsearch.com/carrot2-webapp, based on the top 200 keywords of a PubMed search (Fig. 6a; Chen et al. 2014). Carrot search foam tree offers innovative non-rectangular tree map layouts. Visually pleasing non-rectangular layouts efficiently use the available space. The size of the rectangle thus represents the frequency of the topic. Seen from Fig. 6a, drug delivery, membrane, tumor, liposomal formulations, and cancer cells are leading topics in liposomes. The lightweight view generated using Carrot provides a useful point of reference so that any substantial discrepancies would be accounted for (Chen et al. 2014).

In this article, we will rely on scholarly publications in the Web of Science as a more rigorous and reliable representation of the literatures. VOSviewer was used to analyze major topics on liposome. In the density view (Fig. 6b), each point in a map has a color that depends on the density of items at that point. By default, this color is somewhere in

Table 7 The 20 most frequently used keywords for the study period

Keyword	Frequency	Keyword	Frequency
Gene	2259	Doxorubicin	468
Drug delivery	1551	Fluorescence	468
Cell	1340	Activity	446
Cancer	1136	Cholesterol	418
Peptide	782	Vaccine	415
Protein	768	Macrophage	408
DNA	722	Antibody	316
Membrane	716	Chitosan	282
PEG	532	Vitro	278
Release	489	Antioxidant	273

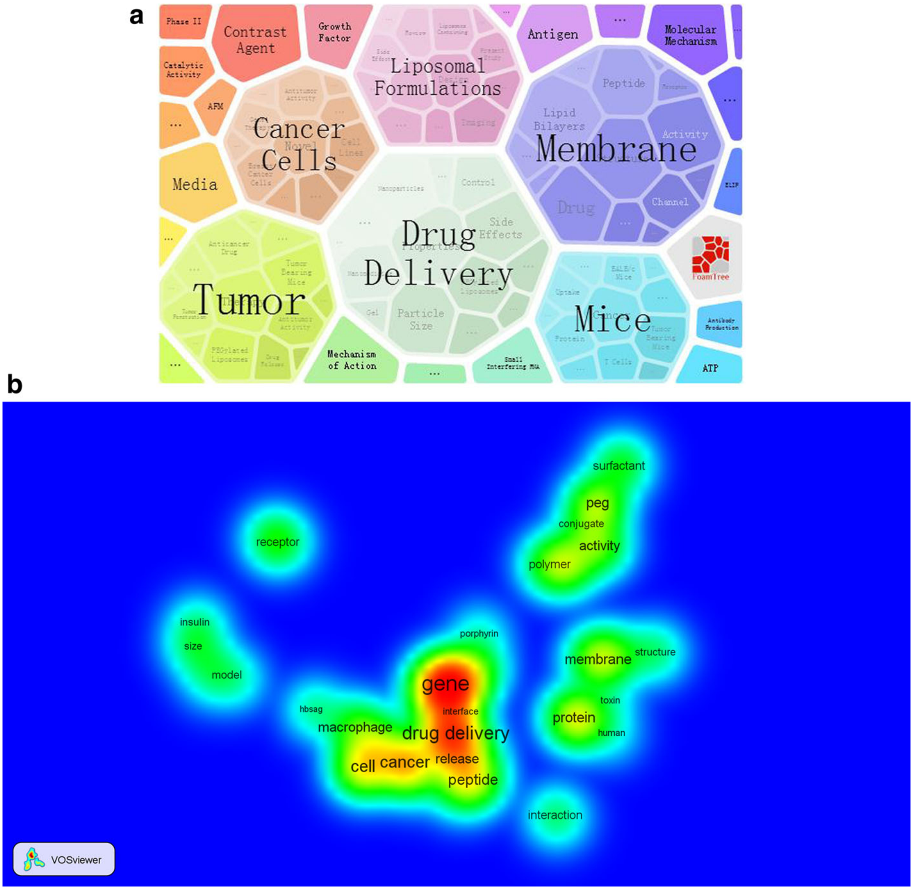

Fig. 6 Pictures of major topics on liposome, based on the top 200 results. **a** Search results from the PubMed. **b** Search results from the SCIE

between red and blue. The larger the number of items in the neighborhood of a point and the higher the weights of the items, the closer the color of the point is to red. Conversely, the smaller the number of items in the neighborhood of a point and the lower the weights of the items, the closer the color of the point is to blue. Seen from Fig. 6b, gene, drug delivery, cell and cancer are leading topics in liposome. (1) Gene therapy has shown great promise for the potential cure of several genetic disorders and appears to possess enormous therapeutic potential. Liposomes are one of the techniques of gene transfer. Liposome mediated gene therapy can be an independent treatment or be used in combination with other treatments. (2) Over the past decades, liposomes became a focal point in developing drug delivery systems. Several drugs and molecules, such as anticancer and antibacterial agents, imaging and probing agents, peptide hormones, proteins, enzymes, and vaccines have been loaded into the aqueous compartment or lipid phases of liposomes (Kraft et al. 2014). Amphotericin B, cytarabine, doxorubicin, daunorubicin, morphine, mifamurtide, propofol, verteporfin, paclitaxel, vincristine, and bupivacaine are examples for commercially available liposomal drug products (Hafner et al. 2014; Kraft et al. 2014). Current research focuses either on actively targeted liposomes or on use of stimuli-sensitive liposomes. (3) Anti-cancer drugs, especially in the liposomal form, can inhibit the growth of tumor cells and may therefore provide a basis for the development of cancer therapies. On the other hand, cell transfection is also an important research hotspot of liposome related cells. Lipofectamine method could get a higher transfection efficiency and higher survival rate for cells in cell transfection. (4) For cancer therapy, the liposome-based system is one of the most established and successful platform technologies. Certain anticancer drugs such as doxorubicin, daunorubicin, paclitaxel, mifamurtide, cytarabine, and vincristine are marketed products provided through liposomes. Subsequent work on improving the therapeutic potential of liposomes for cancer has focused mainly on developing strategies for actively targeting the liposomes to a tumor site, intracellular delivery followed by organelle-specific targeting and triggered release of therapeutic payloads utilizing pathological differences in the tumor's microenvironment. Seen from Fig. 6b, clusters of the four hotspots gather together. Because they relate to multiple objectives, and these objectives are not independent, they are related to each other. At the same time, peptide, protein, membrane, release, fluorescence, activity, cholesterol, vaccine, macrophage, vitro, and antioxidant are also relatively hot research content. These 20 categories are both mutually independent and connected each other, and they constitute the research hotspots of liposome together.

Research trends

Burst detection using CiteSpace can identify burst keywords as indicators of emerging trends over time (Fig. 7). Keyword categories of publications in the SCIE database (1995–2014) were analyzed for their burst. The time interval is depicted as a blue line. The period time in which a keyword category was found to have a burst is shown as a red line segment, indicating the beginning year and the ending year of the duration of the burst. For example, at the top of the list, keyword "nanoparticles" has a period of burst between 2010 and 2014 with burst strength of 253.9043.

Seen from Fig. 7, hot areas prior to 2003 belong to three fields: (1) preparation and characterization of liposomes, including in vivo, in vitro, lipid peroxidation, and phosphatidylcholine. (2) Gene, including gene therapy, gene transfer, and expression. (3) Adriamycin: Since the approval of a liposome-based adriamycin pharmaceutical product in 1995 by the US Food and Drug Administration (FDA), liposome research of adriamycin have increased dramatically (Barenholz 2012; Chang and Yeh 2012; Jabir et al. 2012; Kraft et al. 2014).

Topics after 2008 mainly belong to nanotechnology, drug delivery, siRNA, and cancer therapy. (1) Nanotechnology: Nanoparticles, nanomedicine, nanocarriers and nonotechnology have very strong burst since 2009. The ability of nanosized liposomes to provide targeted drug delivery, improve drug solubility, extend drug half-life, improve a drug's therapeutic index, and reduce a drug's immunogenicity has resulted in the potential to revolutionize the treatment of many diseases (Honda et al. 2013; Ramos-Cabrer and Campos 2013; Hafner et al. 2014; Kraft et al. 2014). (2) Drug delivery: Liposomes have now progressed beyond simple, inert drug carriers and can be designed to be highly responsive in vivo, with active targeting, increased stealth, and controlled drug-release properties. The challenge of liposomal drug delivery is to combine all of these design factors in a rational manner to ultimately achieve optimal therapeutic outcome in the clinic.

Keywords	Year	Strength	Begin	End	1995 - 2014
nanoparticles	1995	**253.9043**	2010	2014	
invivo	1995	**186.3961**	1995	2000	
drug-delivery	1995	**159.0927**	2011	2014	
gene therapy	1995	**79.3704**	1997	2003	
invitro	1995	**72.5338**	1995	1999	
expression	1995	**46.8785**	1997	2000	
gene transfer	1995	**46.8772**	1996	2003	
nanomedicine	1995	**42.7925**	2009	2014	
nanocarriers	1995	**40.4626**	2009	2014	
sirna	1995	**38.3062**	2008	2014	
adriamycin	1995	**35.6585**	1995	1999	
cancer-therapy	1995	**35.4321**	2011	2014	
lipid peroxidation	1995	**33.9478**	1995	2001	
efficient	1995	**33.6492**	1996	2000	
phospholipid-vesicles	1995	**32.6708**	1995	1999	
cystic-fibrosis	1995	**31.5264**	1997	2002	
phosphatidylcholine	1995	**28.9082**	1995	1999	
cancer-cells	1995	**28.6327**	2012	2014	
purification	1995	**28.2157**	1995	1996	
nanotechnology	1995	**27.657**	2009	2014	

Fig. 7 Top 20 keywords with strongest citation burst

(3) SiRNA: The field of small interfering RNAs (siRNAs) as potent sequence-selective inhibitors of transcription is rapidly developing (Reischl and Zimmer 2009). However, its use is limited by inefficient delivery. Safety, effectiveness, and ease of production and manufacturing are important considerations for selecting the appropriate siRNA carriers. Liposome is a good non-viral-based delivery method which has been used for delivering siRNA (Auguste et al. 2008; Chen et al. 2011, 2013). (4) Cancer therapy: Success of Doxil promotes the research and development of liposomes carrying anticancer drug. Further understanding of how actively targeted liposomes behave in vivo and subsequent optimization of liposome design could translate into successful applications of targeted liposomes in the clinic, providing the potential for substantial breakthroughs in cancer therapeutics (Qhattal and Liu 2011; Gray et al. 2013; Deshpande et al. 2013; Yao et al. 2013). Taken together, nanotechnology, drug delivery, siRNA and cancer therapy are trends of liposome.

Conclusions

An evaluation of liposome research trends during 1995–2014 was obtained by statistical analysis of the patterns of characteristics of publication outputs, journals, countries/territories, institutions, authors, research areas, research hotspots and trends. The number of publications per year has increased steadily. The Journal of International Pharmaceutics published the largest number of liposome-related publications.

USA accounts for the largest number of high-quality publications. The USA's dominant position in liposome research is affirmed by housing four research institutions that ranked among the ten most active institutions. The worldwide geographic distribution of authors in liposome-related research was visualized cartographically, with major spatial clusters in the USA, Western Europe, and Asia. To a certain extent, large numbers of research publications from a country are correlated with the high economic level of the country. In our data set from the 20 most active countries/territories, 17 are high-income countries, and the other 3 are middle-income countries (China, India and Brazil). The important research institutes are mainly originated from the USA and Japan. The Osaka Univ (Japan), Kyoto Univ (Japan), and Univ Texas (America) are the three most active institutions. Van Rooijen N (Netherlands) has a top ranking. The collaboration on all scales (authors, and countries) seems to indicate a greater globalization and structuration of the research carried out, with more complex and articulated research networks present. It indicated that research in liposomes had become more globally connected. The increased case of communication in a technologically connected world contributed to the increasing collaboration. It would be reasonable to assume that more international collaboration would lead to more output due to the sharing of ideas and workloads.

Keywords analysis revealed the hotspots in liposome studies, which were gene, drug delivery, cell and cancer. Burst detection results indicate that nanotechnology, drug delivery, siRNA and cancer therapy are trends of liposome.

Bibliometric method could quantitatively characterize the development of global scientific production in a specific research field. As liposome research has always been thought to be widely useful to humans, more efforts should be taken to further study in these fields. Furthermore, this bibliometric research can be used by policy-makers to identify strategies for improving the distribution of resources, and subsequently for optimizing the quantity and quality of liposome research.

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