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Review Article

A Bibliometric Analysis of the Gene Delivery Systems for Lung Cancer from 2010 to 2022

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Abstract

The gene delivery systems (GDS) for lung cancer (LC) has made significant progress over the past 12 years, yet, there is a great challenge in its clinical application due to low delivery efficiency. This study aims to explore research fields related to gene therapy for LC and predict future directions from a bibliometric perspective. The Web of Science Core Collection collects articles and reviews on GDS for LC published from 2010 to 2022. Comprehensive bibliometric and visual analyses were performed using CiteSpace, VOSviewer, R-Bibliometrix, and Microsoft Excel. The analysis showed that the number of publications on GDS for LC has been increasing over the past 12 years, highlighting the growing interest and research efforts in this area. A rigorous examination of keywords and research hotspots revealed that the themes such as "complex," "transfection," "RNA interference," "extracellular vesicle," "co-deliver," "resistance," etc. dominate the field of GDS for LC. These findings indicated that the research in GDS for LC is evolving, with a noticeable shift toward addressing challenges related to delivery efficiency, transfection methods, and overcoming resistance mechanisms in gene therapy. The comprehensive study provides an overview of the literature on GDS for LC and identifies areas that require further exploration and development. By highlighting emerging research hotspots, our bibliometric analysis offers valuable insights to scholars and researchers, aiding in the identification of gaps, and guiding future efforts toward the development of GDS with more efficiency for LC therapy.

Keywords

- lung cancer
- gene delivery system
- Bibliometric analysis

Introduction

Over the last two decades, cancer-related deaths have decreased by almost 26%, resulting in a reduction of 2.4 million deaths.[1] Lung cancer (LC) is the primary reason for cancer-related fatalities globally, accounting for 13.2% of all newly diagnosed cancer cases and contributing to 25.9% of all cancer-related deaths. The average 5-year survival for LC is 18.1%.[2] LC is currently treated with surgery, chemotherapy, and radiotherapy[3]; however, treatment alternatives for patients with LC are very limited, with only 20% of patients responding positively to systemic chemotherapy.[4] Targeted therapies, such as ALK-targeted inhibitors including crizotinib, have been highly successful in LC therapy. Nevertheless, their efficacy is severely limited by the presence of resistance mechanisms.[5] Gene therapy is helpful for the identification of genes implicated in the cause of the disease, which has the potential to deepen our understanding of the underlying mechanisms, and

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ultimately pave the way for the development of additional strategies for prevention and targeted treatments. Yet, gene therapy for LC progressed slowly in the clinic due to low delivery efficiency and potential cytotoxicity. Thus, we need a more comprehensive understanding of gene delivery systems (GDS) and the development of effective delivery approaches that incorporate new theories and methods to achieve successful clinical translation of GDS in LC therapy.

Bibliometrics is a subfield of informatics that focuses on assessing the current state and future trends in research development. Mapping knowledge domains with professional software tools provides intuitive results. Before that, data must be retrieved from a database, processed, clustered to reduce dimensions, and organized into a network consisting of nodes and links. Networks can be categorized as co-occurrence, co-citation, or collaboration networks, depending on the items of interest and their relationships, which reveal connections between keywords, references, or authors, offering insights into the research field. Keywords within the same article often share a relationship within a specific discipline and can be linked to form a co-occurrence network. Similarly, references cited by the same article are connected in a co-citation network.

CiteSpace is a software tool for co-citation analysis and is crucial in identifying trends and developments in scientific domains. Its design is based on scientometric citation analysis theory, blending social networks and complex network analysis to construct citation networks. These networks form the core of CiteSpace's knowledge maps, revealing interconnections within academic literature. Using mathematical and computational methods, CiteSpace analyzes citations and references to trace the flow of knowledge units, uncovering patterns in the dissemination of knowledge across scholarly works. The clustering algorithm used primarily relies on nominal terms to identify hotspots in academic research. This approach helps to identify pivotal terms in maps, enabling the analysis of research hotspots, and guiding

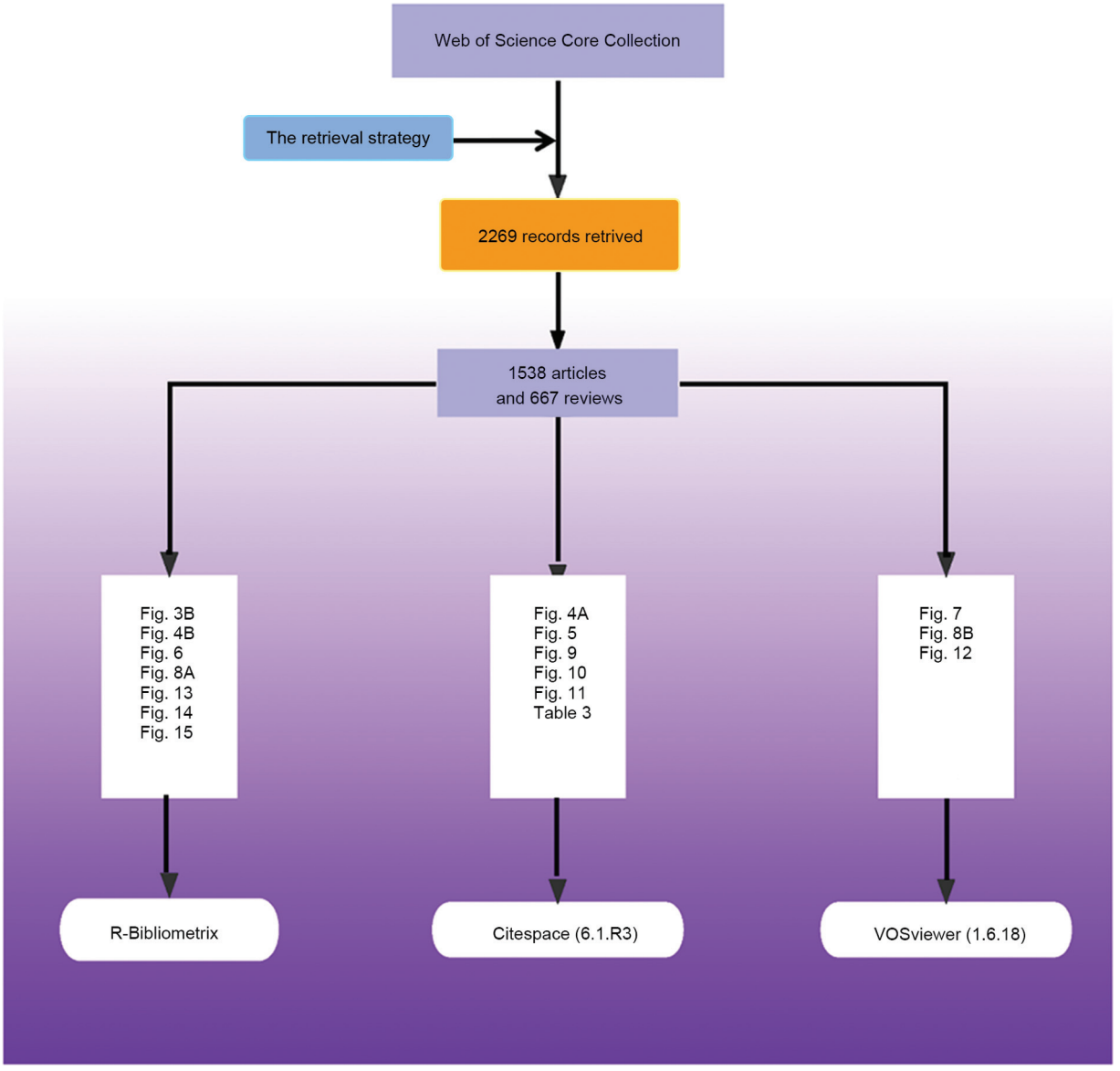


Fig. 1 Research flow diagram of this study.

the direction of study. In contrast, VOSviewer's clustering algorithm is based on the strength of associations, selecting high-frequency keywords from texts for cluster analysis. The technique employed in this research reflects the research themes of the discipline through high-frequency keywords and utilizes a distance-based visualization method. This method defines the relative positions of texts and creates maps with a strong knowledge map representation.

In addition, the alluvial flow diagram, presented by MapEquation, a web-based application, helps illustrate changes in the network over time. This offers intuitive insights into the tendencies of a field. By combining bibliometrics with data visualization, it is possible to quantitatively and graphically build a knowledge structure of a given domain. This combined approach is pivotal in evaluating literature performance, identifying central issues, and understanding disciplinary challenges, providing a comprehensive and dynamic view of the research landscape.[6]

To the best of our knowledge, no bibliometric analysis of GDS for LC has been conducted yet. In this study, the Web of Science Core Collection (WOSCC) database was utilized to analyze research trends, quantity of publications, citations, and keywords that are prominent in GDS for LC. We also identified research hotspots in LC gene therapy and predicted its future trends. Besides, we used CiteSpace and VOSviewer to simplify the literature, which helps us gain insights into the current state of research and future directions in this field. ►**Fig. 1** presents the research flow chart of this study.

Material and Methods

Data Sources and Search Strategies

WOSCC (https://www.webofscience.com) was used for publication correction. The retrieval strategy was as follows: [(Gene therapy OR Gene delivery OR Targeted Gene Delivery) AND lung cancer]. Only publications written in English were included in the analysis, and the document types were limited to "article" and "review." The data category was limited to "Pharmacology & Pharmacy." Afterward, we evaluated the titles and abstracts of the articles to determine their relevance to the topic of gene therapy in LC over the past 12 years (2010–2022). The full text was downloaded and evaluated in detail for the uncertain literature. The search was conducted on a specific day to mitigate any bias resulting from the daily database update.

Bibliometric Analysis

CiteSpace (6.1.R3, https://citespace.podia.com) was used to visualize research frontiers, knowledge bases, periods, and key literature that play a role in the evolution of research. It focuses on identifying critical junctures in the development of a field or domain, particularly intellectual turning points and pivotal moments.[7]

VOSviewer (1.6.18, https://www.vosviewer.com) was employed to create visual representations of the co-citation network among authors and journals, as well as the co-occurrence of keywords. The generated visual map shows nodes representing authors, journals, keywords, and other entities. Node size indicates the frequency of occurrences, line thickness indicates connection strength, and node color indicates different clusters or periods.

R-Bibliometrix was used to conduct analyses, including a study of the evolution of themes based on keywords over time, visualizing cooperation networks between countries, and analyzing the publishing characteristics of journals. Additionally, R software (https://www.r-project.org) and R-Bibliometrix (https://www.bibliometrix.org/home/) were used to generate distribution maps illustrating the temporal changes in high-frequency keywords.

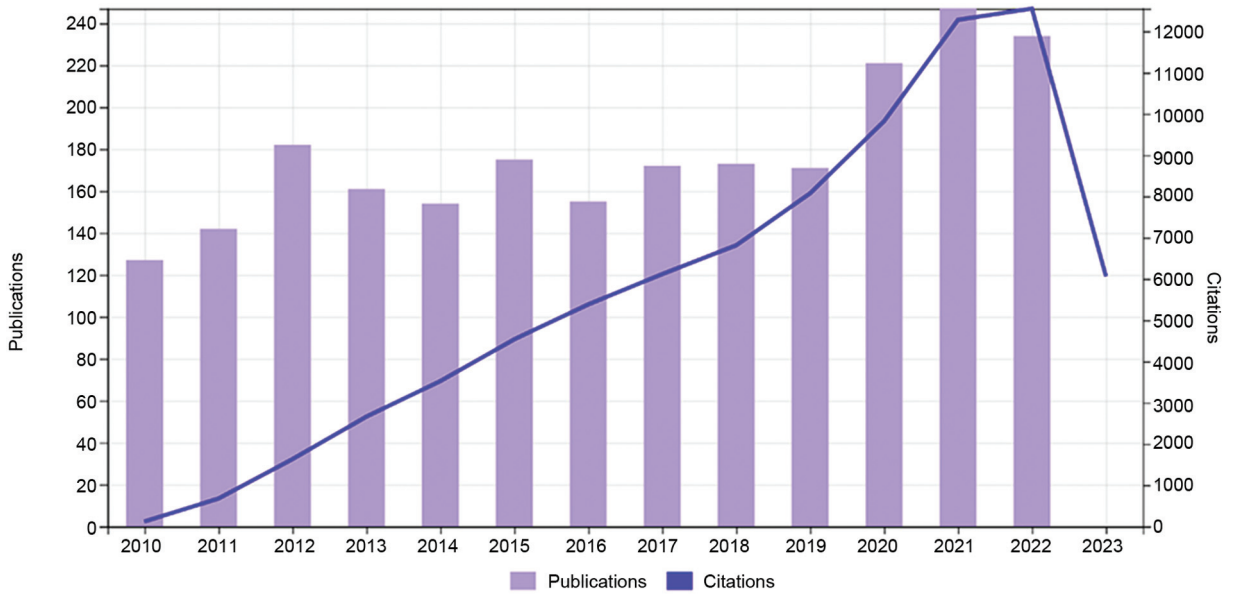


Fig. 2 Number of annual publications regarding GDS for LC from 2010 to 2022 generated by WOSCC. Each bar represents the annual publication count. The dashed line represents the trend curve fitting for this pattern. GDS, gene delivery systems; LC, lung cancer.

Results and Discussion

Annual Publications and Trend

The count of articles published each year is an important indicator of research trends and the rate of knowledge advancement in the field.[8] In this work, a bibliometric analysis was conducted. The analysis encompassed a total of 2,314 publications related to GDS for LC. As shown in ►**Fig. 2**, research activities have continued to increase since 2012 with 2021 being marked the peak. Despite occasional fluctuations in specific years like 2014 and 2016 that may reflect changes in research focus, funding landscapes, etc., the overall trend indicated a growing interest in GDS for LC. These publications collectively garnered 78,058 citations with an average of 34.68 citations per paper, and an H-index of 117, highlighting the significant impact and relevance of GDS in the realm of LC. In addition to quantitative data, we have delved into the content and themes of these publications, which revealed the evolving research focus and highlighted the increasing prominence of gene therapy in LC treatment. This shift toward targeted therapeutic is reflected in the rising number of articles focusing on GDS, suggesting a trajectory of research and development in the field.

Countries/Regions

The United States, China, and Japan are the leading contributors in the area of GDS for LC. Specifically, the United States has been at the forefront with 696 publications, accounting for 30.078% of the total and garnering 26,502 citations with an average of 48.10 citations per paper. The analysis shows that the research output in the field of GDS is dominated by the United States, followed by China with 640 publications, accounting for 23.336% of the total and 12,882 citations with

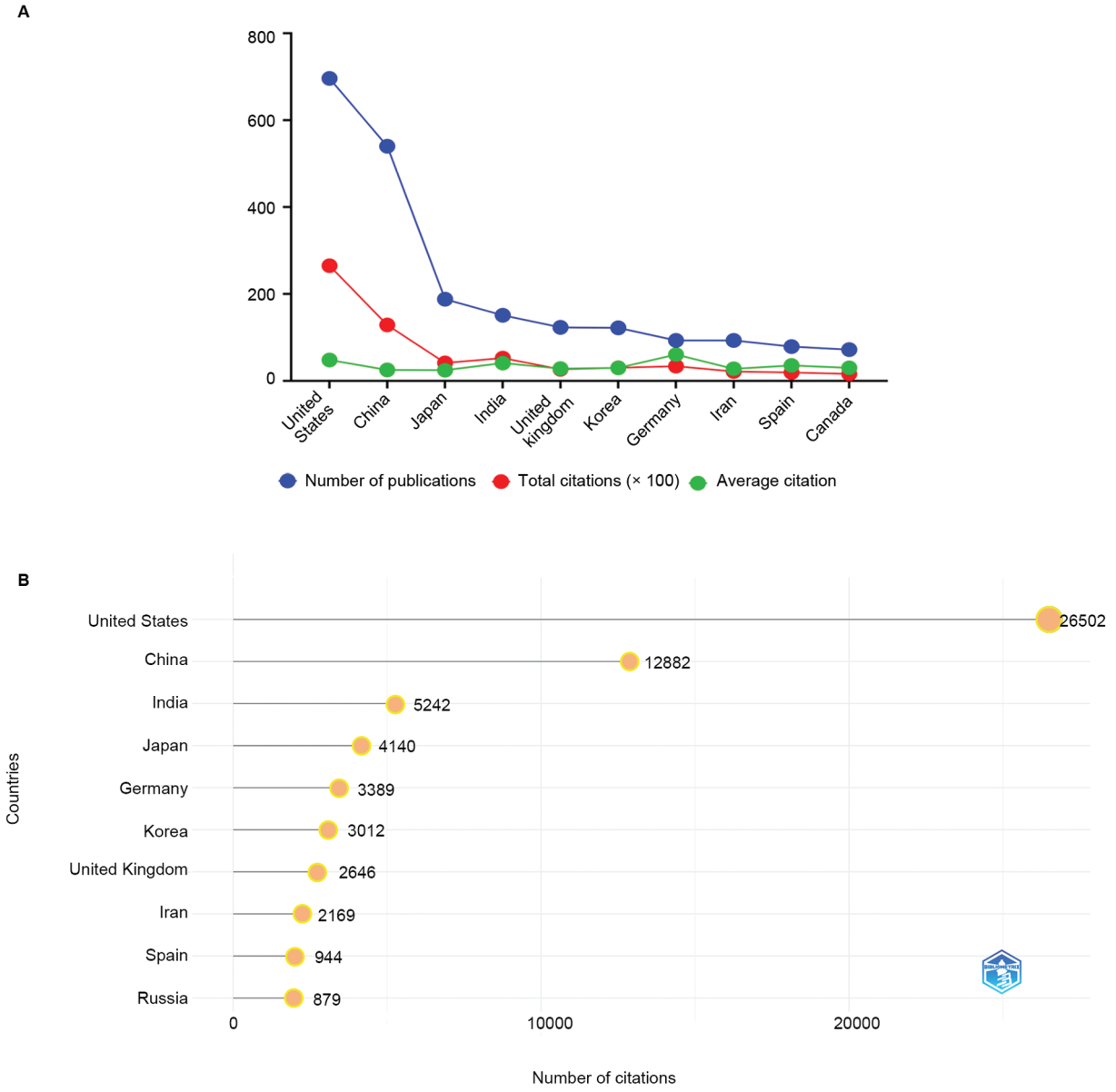
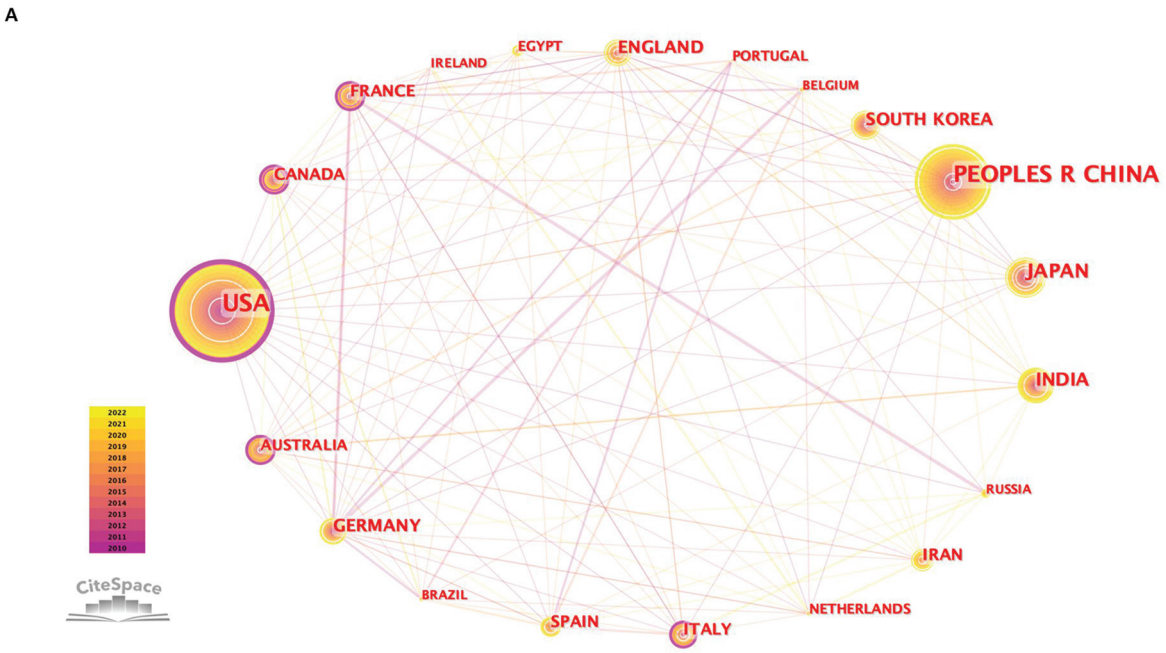
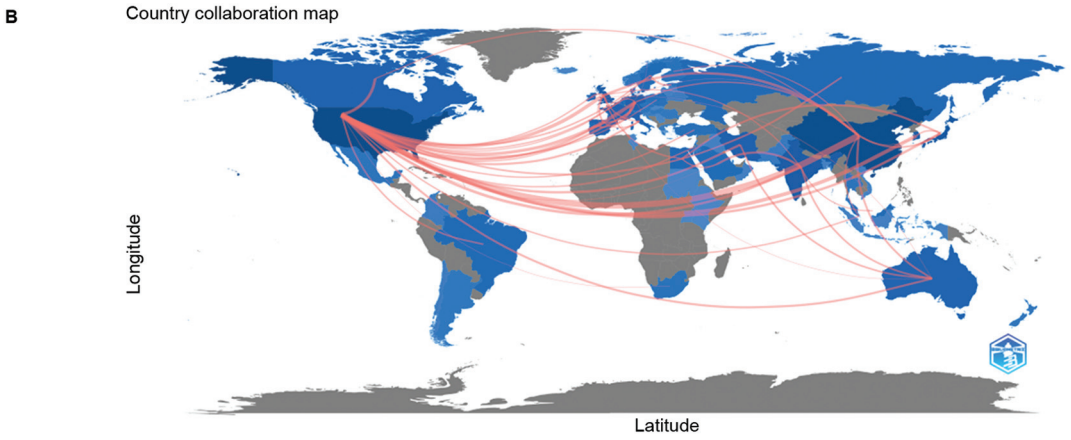


Fig. 3 Numbers of annual publications of the top 10 productive countries. (**A**) The publication count, total citations, and average citations per article of the 10 most productive countries/regions. (**B**) R-Bibliometrix generates the citation count of the top 10 most cited countries.

an average of 25.26 citations per paper. This suggests that China has made a substantial contribution to the field of GDS, likely due to its investment in biotechnology and potential leadership in specific technological aspects of GDS. Japan also contributed significantly to the research with 188 publications and 8.124% of the total, accumulating 5,242 citations at an average of 40.95 citations per paper. This can be attributed to their expertise in precision medicine or nanoparticle-based drug delivery systems (►**Fig. 3A, B**).

The patterns of collaboration, as depicted by CiteSpace and R-Bibliometrix, revealed more than just the volume of collaboration; the thickness of the lines and the red-colored lines between countries indicated that there are concentrated efforts in areas such as nonviral delivery systems or immunotherapy approaches. Particularly, the United States and China showed the highest number of collaborations with other countries/regions (►**Fig. 4A**). This extensive collaboration network, especially among the





Rank	From	To	Frequency
1	United States	China	72
2	United States	Korea	25
3	United States	United Kingdom	23
4	United States	Germany	19
5	United States	Canada	16
6	United States	India	16
7	China	United Kingdom	14
8	United States	Japan	13
9	United States	France	12
10	United States	Iran	11

Fig. 4 National collaborative network. (**A**) National collaborative network generated by CiteSpace. Each node represents a country, and its size is proportional to the number of publications. The links between countries indicate co-occurring relationships and their thicknesses reflect the strength of the collaboration. (**B**) GDS country collaboration map generated by R-Bibliometrix. GDS, gene delivery systems.

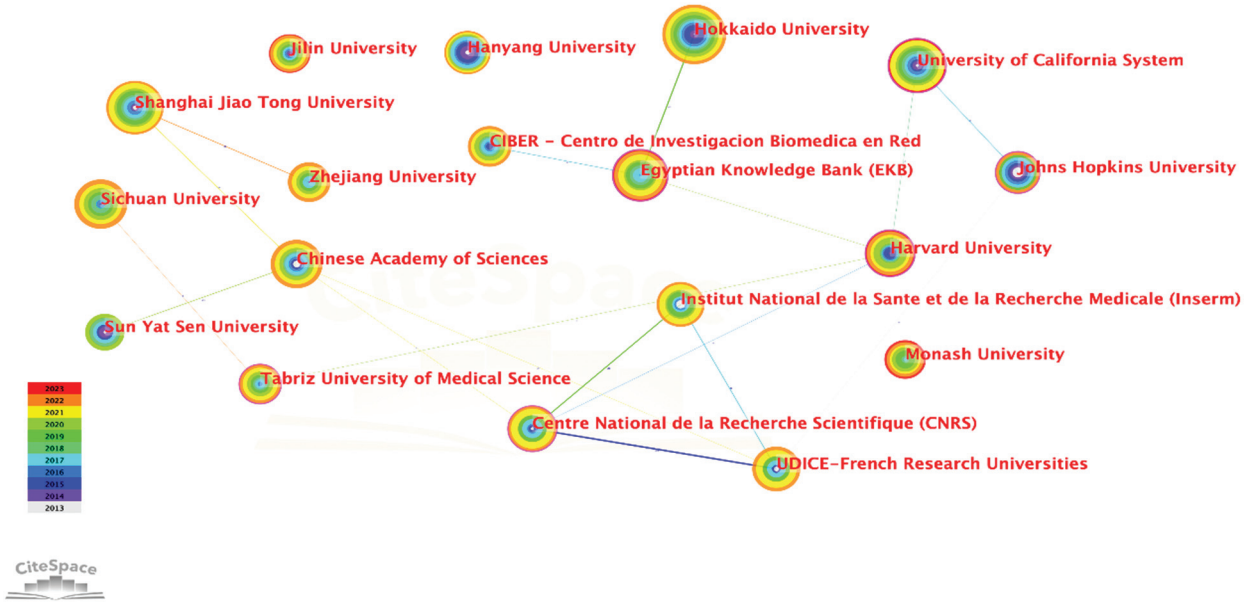


Fig. 5 CiteSpace generates a cooperation network of institutions. Each node represents an institution, whose size is proportional to the number of publications. Links between nodes represent the strength of collaboration.

United States, European countries such as Germany and France, and Asian countries such as China, Japan, and South Korea, formed the core of the national cooperation map in GDS for LC research (►**Fig. 4B**). However, there is a clear gap in global research collaboration, particularly the lower level of cooperation with developing countries, demonstrating the need of more inclusive and diverse international research partnerships.

This analysis provided LC with a comprehensive understanding of the global landscape in GDS research. It not only highlighted substantial contributions and collaborations but also delved into the unique strengths and focuses of research

Table 1 Ranking of the top 18 institutions with the most publications

Rank	Institution	Country	No. of publications	BC
1	Hokkaido University	United States	55	0.06
2	University of California System	United States	45	0.19
3	Shanghai Jiao Tong University	China	41	0.07
4	Sichuan University	China	41	0.08
5	Centre National de la Recherche Scientifique (CNRS)	France	37	0.12
6	Egyptian Knowledge Bank (EKB)	Egyptian	35	0.19
7	Institut National de la Sante et de la Recherche Medicale (Inserm)	France	35	0.06
8	UDICE-French Research Universities	France	34	0.02
9	Chinese Academy of Sciences	China	33	0.06
10	Harvard University	United States	31	0.22
11	Johns Hopkins University	United States	27	0.12
12	Hanyang University	South Korea	27	0.03
13	University of London	United Kingdom	24	0.12
14	University of Texas System	United States	24	0.14
15	N8 Research Partnership	United Kingdom	23	0.14
16	Sun Yat Sen University	China	23	0.01
17	CIBER - Centro de Investigacion Biomedica en Red	Spain	22	0.06
18	Kyoto University	Japan	22	0.05

Abbreviation: BC, betweenness centrality.

Table 2 Top 10 journals with the most publications regarding GDS for LC

Journals	No. of publications	Total citations	IF (2022)	JCR (2022)
Journal of Controlled Release	332	7,153	10.8	Q1
International Journal of Nanomedicine	176	1,338	8.1	Q1
Molecular Pharmaceutics	151	1,623	4.9	Q1
International Journal of Pharmaceutics	148	2,491	5.8	Q1
Pharmaceutics	121	439	5.4	Q1
Advanced Drug Delivery Reviews	72	2,989	16.1	Q1
Pharmaceutical Research	65	1,306	3.7	Q2
Expert Opinion on Drug Delivery	62	654	6.6	Q1
Journal of Drug Targeting	53	688	4.5	Q2
Current Pharmaceutical Design	48	306	3.1	Q3

Abbreviations: GDS, gene delivery systems; LC, lung cancer.
JCR stands for Journal Citation Reports, which is a comprehensive resource that provides information about the citation performance of academic journals. The classification criteria for Q1, Q2, Q3, and Q4 are as follows: Q1, journals in the top 25% (including 25%) based on their impact factor; Q2, journals with impact factors ranging from 25% to 50% (including 50%); Q3, journals with impact factors ranging from 50% to 75% (including 75%); Q4, journals with impact factors below the 75th percentile.

of the leading countries. These insights provided a clear picture of the current hotspots, collaborative trends, and potential areas for further exploration in GDS for LC research.

Institutions

A comprehensive examination of 2,314 publications from 400 institutions worldwide, as illustrated by the CiteSpace-

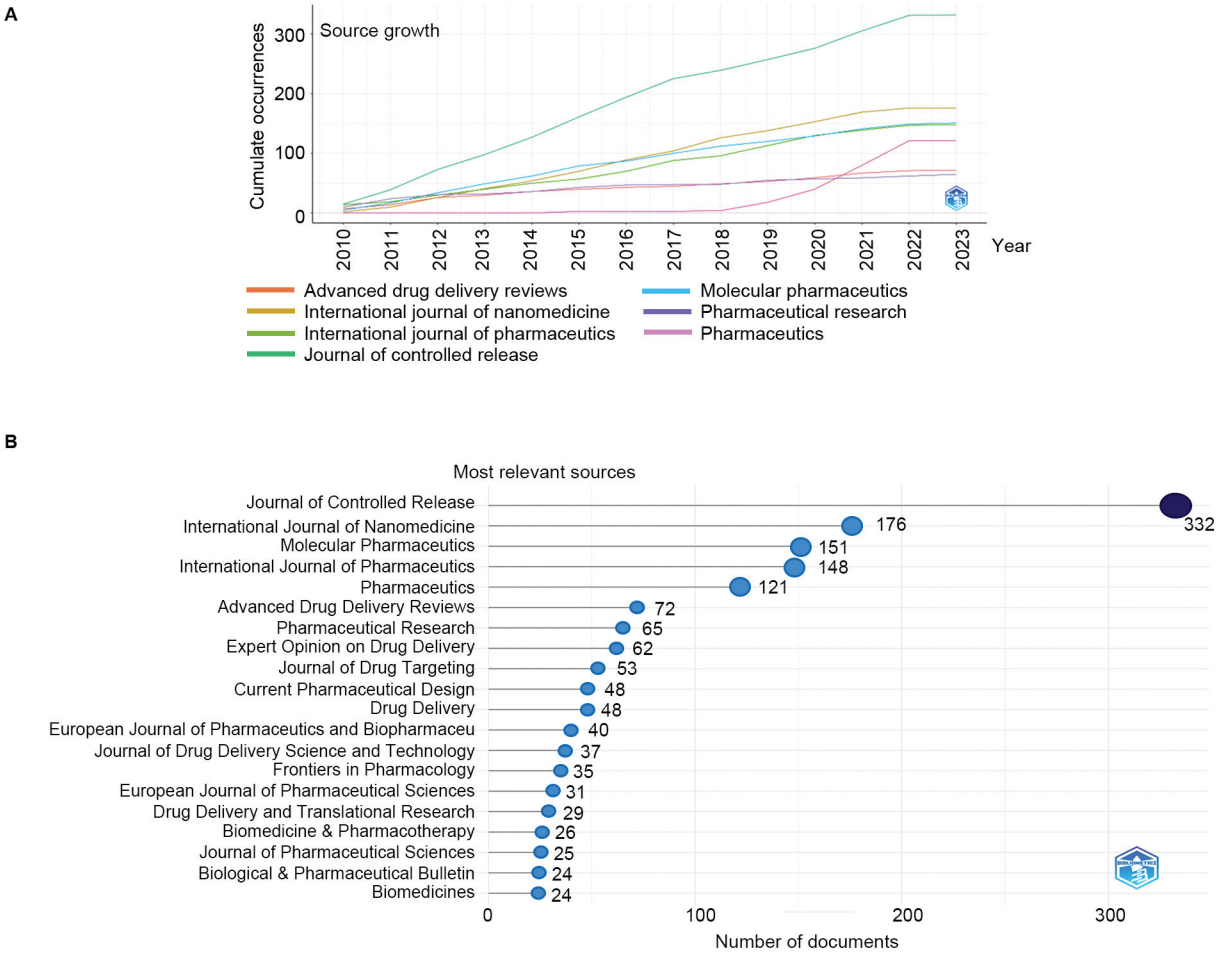


Fig. 6 (A) R-Bibliometrix generates annual occurrences of the top seven journals with the most publications. (B) The top 20 most influential journals in terms of publications on GDS. GDS, gene delivery systems.

generated network in ►**Fig. 5**, revealed more than just the volume of scholarly contributions. This analysis highlighted the central role these institutions played in advancing GDS research. Key institutions such as Hokkaido University, the University of California System, Shanghai Jiao Tong University, Sichuan University, and the Centre National de la Recherche Scientifique (CNRS) stood out not only for their number of publications but also for their influential

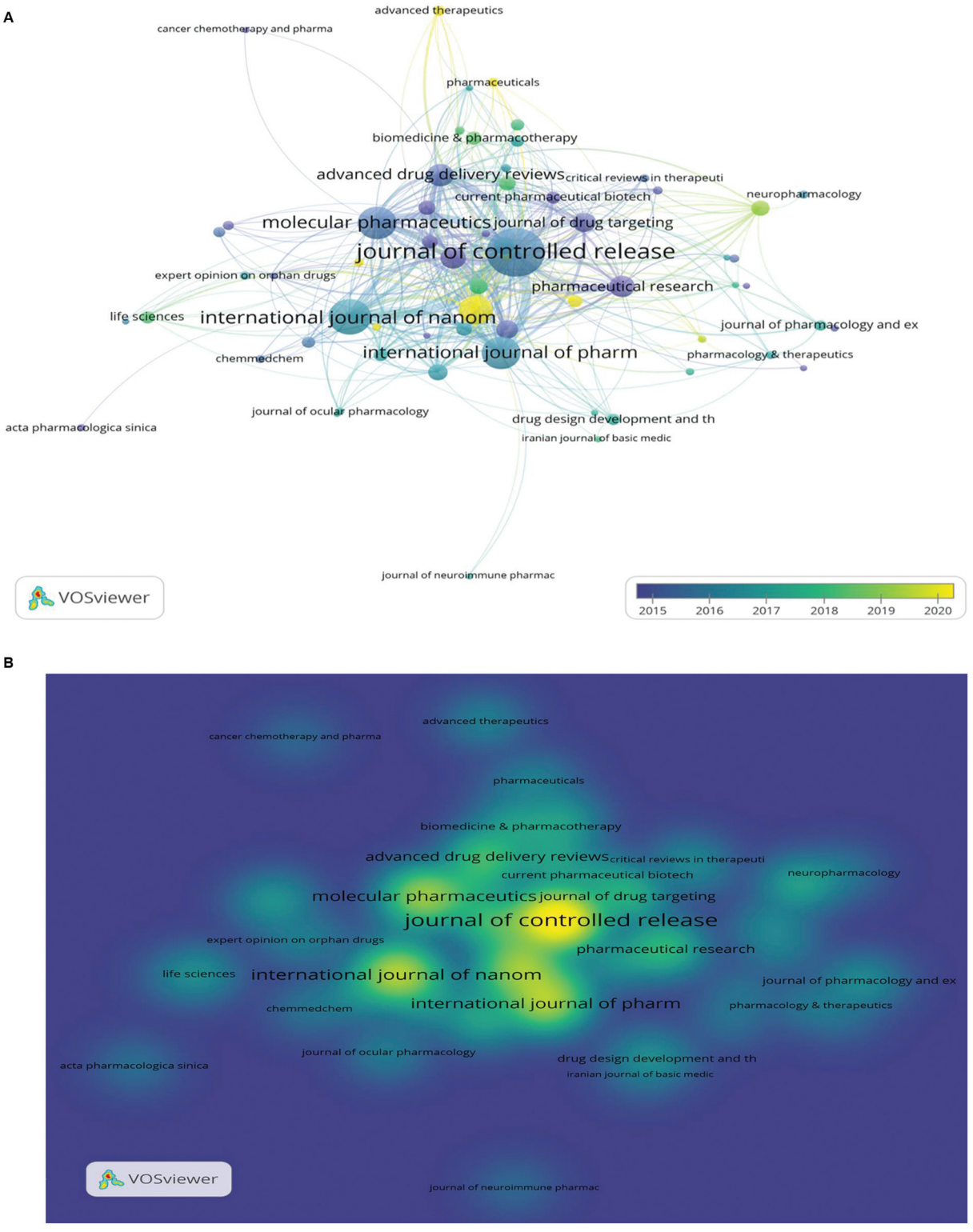


Fig. 7 (A) VOSviewer generates the network visualization diagram of journal citation analysis. Each node represents a journal, and the area represents the citation frequency. Its size reflects the number of citations. (B) Density map of the journal citation network of nanoparticles in gene delivery. A higher density means that the nodes are closer to each other, and the number of neighboring nodes is higher. The map's color ranges from yellow (high density) to green (low density).

positions in the collaborative network, as indicated by their significant betweenness centrality (BC) values (a BC value >0.1 is considered crucial[9]). For instance, as shown in ►**Fig. 5** and ►**Table 1**, the University of California System, with a BC value of 0.19, and Harvard University with 0.22, transcended their roles as prolific publishers and emerged as central nodes facilitating multidisciplinary research. This was particularly evident in their potential contributions to innovative areas such as targeted delivery mechanisms and the development of nonviral vectors. Of the top 18 contributors, five institutions are from the United States (►**Table 1**), confirming the strong presence of American institutions in the field of research and highlighting the important role of the United States in leading GDS research. As shown in ►**Fig. 5**, the depth and nature of the collaborations, particularly among institutions with high BC values, highlighted the coordinated efforts in LC therapy in addressing the intricate challenges. This trend of collaboration reflects the concentration of research efforts on emerging hotspots in GDS in the LC landscape, underscoring the dynamic nature of this research area and the collective drive toward innovative solutions in LC therapy.

Journals

In total, 204 journals published a total of 2,314 papers, of which 25 journals published more than 20 papers each. The

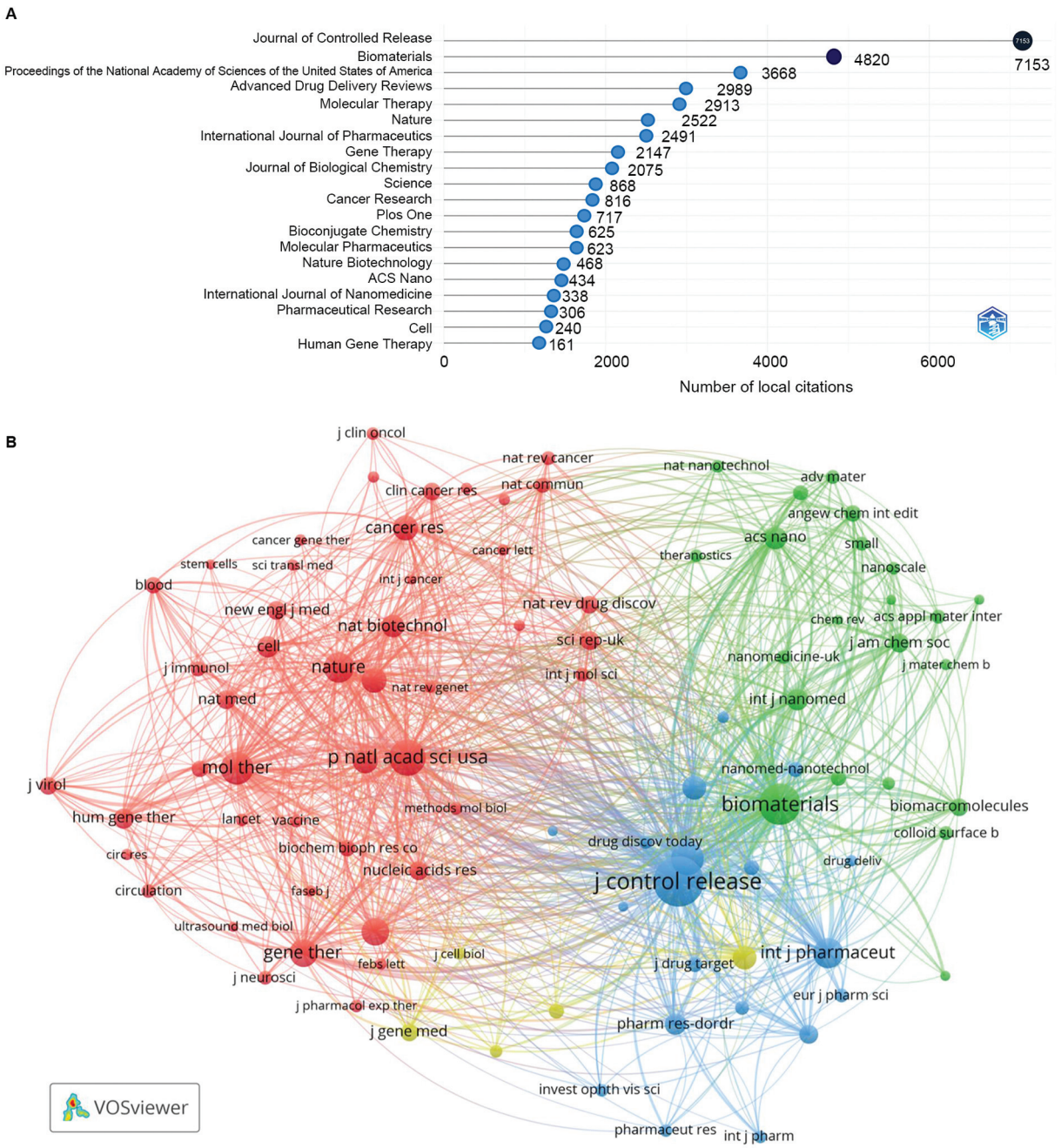


Fig. 8 (A) R-Bibliometrix generating the top 20 journals in terms of co-citation. (B) VOSviewer generates the network visualization diagram of the journal co-citation.

leading journal was "Journal of Controlled Release" with 332 publications, followed by the "International Journal of Nanomedicine" with 176 publications. The high citation numbers, such as 7,153 citations for the Journal of Controlled Release, suggested that these journals were key in disseminating influential research on GDS for LC (►**Table 2**).

R-Bibliometrix created occurrence maps each year (►**Fig. 6**) and VOSviewer created network visualizations of journal citation (►**Fig. 7**). This highlighted publication trends and the interconnectedness of the journals in research landscape. The network visualization diagram of the journal co-citation analysis revealed that the "Journal of Controlled Release" and PNAS (Proceedings of the National Academy of Sciences) were central to the dissemination of core research in GDS for LC, suggesting their significant influence in shaping research directions in the field (►**Fig. 8**).

Journal co-citation regarding GDS for LC was investigated. Additionally, the association of journals such as the "Journal of Drug Targeting" and the "International Journal of Pharmaceutics" with the "Journal of Controlled Release" in co-citation analysis (►**Fig. 8**) indicated specific research areas at the forefront of GDS for LC research. This pattern of co-citation underscored the interconnectedness of research topics and provided insights into the focus area and emerging trends in GDS for LC. This refined analysis thus provided not only a quantitative account of the contributions of various journals but also a deeper understanding of their role in shaping and reflecting the research hotspots and trends within the GDS for the LC field.

Dual-Map Overlays of GDS for LC

The use of dual-map overlays could offer a comprehensive view of the scientific impact in the field of GDS for LC. This technique allows for a visual representation of citation relationships, providing valuable insights into knowledge flow and citation trajectory in the field (►**Fig. 9**).

In the dual-map overlay, the left panel shows the journals in which research papers citing GDS for LC were primarily published. These journals focus on molecular biology and immunology, indicating that GDS research for LC is heavily influenced by and contributes to these areas of science. This also suggests a strong interdisciplinary connection, where advances in molecular biology and immunology directly inform and are informed by the GDS research for LC. On the right panel, the overlay showed that the most cited articles were published in journals focused on chemistry, materials science, and physics, indicating that the foundational and methodological aspects of GDS for LC are rooted in these fields. The high citation rates in such fields demonstrated that GDS for LC research is not only interdisciplinary but also has a significant impact across scientific fields, particularly in understanding and developing the materials and chemical processes fundamental to GDS.

Colored lines representing citation relationships further highlight the knowledge flow between these fields. This suggested a confluence of research in the fields of molecular biology, immunology, chemistry, materials science, and physics that contributes to the development of GDS for LC. The interdisciplinary nature of citations underscored the complex and collaborative nature of GDS for LC research, as discoveries in one field drive advances in another. In light of the above, the dual-map overlay analysis reveals the multidisciplinary impact and citation dynamics in GDS for LC research, underscoring the interconnectedness of the field with various scientific disciplines. This not only reflects the current status of research but also points to future directions where cross-disciplinary collaborations may be critical.

Co-cited References

In the co-cited references' visualization network, the total nodes representing the references were classified into 16 specific clusters with the highest K values, including "#0 anticancer drug," "#1 lipid nanoparticles," "#2 local delivery," and "#3 emerging platform," etc. (►**Fig. 10A**). The timeline view provides insights into the evolution of the field. In ►**Fig. 10B**, the timeline for the 16 clusters is visualized with "RNA interference" and "chitosan" being prominent topics in the early stages of GDS for LC research. However, new fields such as "lipid nanoparticles," "exosomes," and "cas9" were noticed in the context of GDS for

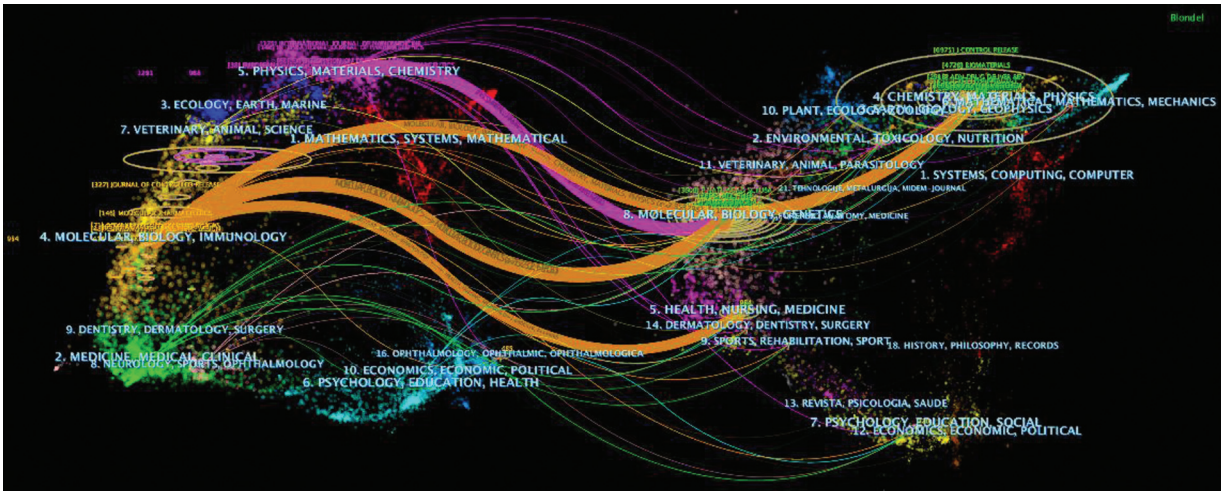


Fig. 9 The dual-map overlay of journals related to GDS research in the cancer field. Co-cited references and the most robust citation burst.

LC from 2015 to 2022. These highlight the evolving nature of research in the field and the shift in emphasis towards these emerging areas.

Reference citation burst refers to references that other studies have cited over a period, which means that they have received special attention in a certain period.[10] In this work, we identified the top 30 references with the most significant citation bursts (►**Fig. 11**), which is listed in ►**Table 3**. As shown in ►**Table 3**, since 2010, the highest citation bursts came from Yin et al's article[11] in 2014 (Strength: 19.34), followed by Whitehead et al's article[12] in Nature Reviews Drug Discovery in 2009 (Strength: 13.35), and Davis et al's article[13] in Nature in 2010 (Strength: 10.52).

Keywords

The network visualization of the keywords generated by VOSviewer is presented in ►**Fig. 12**(**A** and **B**); out of the 11,495 keywords, we included 441 keywords in the analysis,

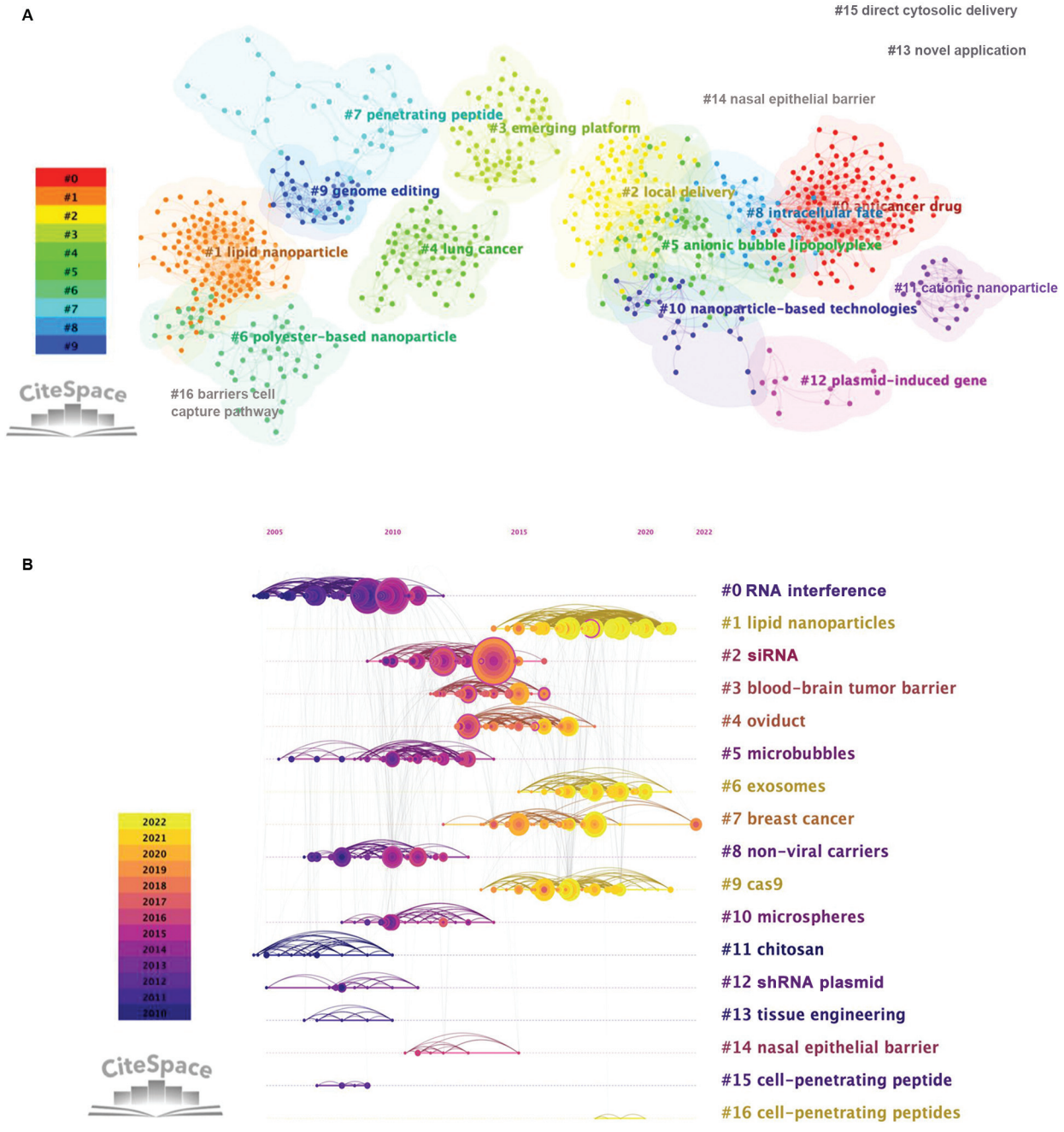


Fig. 10 Co-cited references regarding GDS for LC. (**A**) CiteSpace produces the network diagram of co-citation references. Each node represents a reference, and nodes of the same hue belong to a thematic cluster. (**B**) CiteSpace produces the chronological map of co-cited references' analysis. The diagram depicts the differences in the time of emergence for 18 clusters (2010–2022). The position of each node on the horizontal axis represents the time of initial appearance, the size of nodes represents the total number of citations, and nodes on the same line represent a cluster with a common theme; the links between the nodes illustrate co-citation relationships.

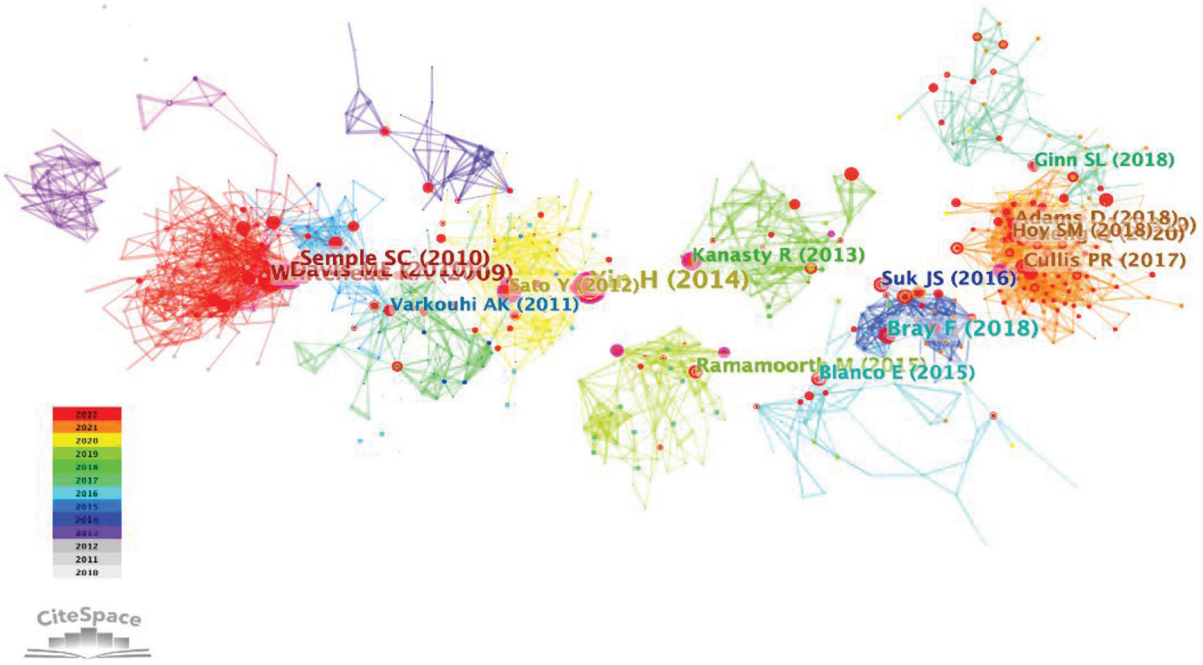


Fig. 11 CiteSpace generating citation burst view map of co-cited references' analysis. Each red node represents one burst.

Table 3 Top 30 references with the strongest citation bursts regarding GDS for LC

References	Year	Strength	Begin	End	2010–2022
Whitehead KA, et al. Nat Rev Drug Discov. DOI: 10.1038/nrd2742	2009	13.35	2010	2014	
Akhtar S, et al. J Clin Invest. DOI: 10.1172/JCI33494	2007	7.37	2010	2012	
Morille M, et al. Biomaterials. DOI: 10.1016/j.biomaterials.2008.04.036	2008	6.99	2010	2013	
Mintzer MA, et al. Chem Rev. DOI: 10.1021/cr800409e	2009	6.99	2010	2013	
Kim DH. Nat Rev Genet. DOI: 10.1038/nrg2006	2007	5.89	2010	2012	
Davis ME, et al. Nature. DOI: 10.1038/nature08956	2010	10.52	2011	2015	
Oh YK. Adv Drug Deliver Rev. DOI: 10.1016/j.addr.2009.04.018	2009	6.93	2011	2013	
Semple SC, et al. Nat Biotechnol. DOI: 10.1038/nbt.1602	2010	10.28	2012	2015	
Love KT, et al. P Natl Acad Sci USA. DOI: 10.1073/pnas.0910603106	2010	5.73	2012	2015	
Pecot CV, et al. Nat Rev Cancer. DOI: 10.1038/nrc2966	2011	8.13	2013	2015	
Varkouhi AK, et al. J Control Release. DOI: 10.1016/j.jconrel.2010.11.004	2011	7.97	2013	2016	
De Ilarduya CT, et al. Eur J Pharm Sci. DOI: 10.1016/j.ejps.2010.03.019	2010	7.11	2013	2015	
Mao SR. Adv Drug Deliver Rev. DOI: 10.1016/j.addr.2009.08.004	2010	6.6	2013	2015	
Akinc A, et al. Mol Ther. DOI: 10.1038/mt.2010.85	2010	5.72	2013	2015	
Sato Y, et al. J Control Release. DOI: 10.1016/j.jconrel.2012.09.009	2012	7.69	2014	2017	
Ginn SL. J Gene Med. DOI: 10.1002/jgm.2698	2013	5.96	2014	2016	
Hatakeyama H, et al. Adv Drug Deliver Rev. DOI: 10.1016/j.addr.2010.09.001	2011	5.96	2014	2016	
Yin H. Nat Rev Genet. DOI: 10.1038/nrg3763	2014	19.34	2015	2019	
Kanasty R, et al. Nat Mater. DOI: 10.1038/NMAT3765	2013	8.67	2015	2018	
Ramamoorth M, et al. J Clin Diagn Res. DOI: 10.7860/JCDR/2015/10443.5394	2015	10.17	2017	2020	
Blanco E, et al. Nat Biotechnol. DOI: 10.1038/nbt.3330	2015	9.87	2018	2020	
Naldini L. Nature. DOI: 10.1038/nature15818	2015	6.4	2018	2020	
Wilhelm S. Nat Rev Mater. DOI: 10.1038/natrevmats.2016.14	2016	5.73	2018	2022	

Table 3 (*Continued*)

References	Year	Strength	Begin	End	2010–2022
Bray F. Ca-Cancer J Clin. DOI: 10.3322/caac.21492	2018	7.96	2019	2022	
Adams D, et al. New Engl J Med. DOI: 10.1056/nejmoa1716153	2018	6.98	2020	2022	
Cullis PR et al. Mol Ther. DOI: 10.1016/j.ymthe.2017.03.013	2017	6.98	2020	2022	
Suk JS, et al. Adv Drug Deliver Rev. DOI: 10.1016/j.addr.2015.09.012	2016	6.59	2020	2022	
Dunbar CE, et al. Science. DOI: 10.1126/science.aan4672	2018	6.55	2020	2022	
Ginn SL. J Gene Med. DOI: 10.1002/jgm.3015	2018	6.34	2020	2022	
Shi JJ. Nat Rev Cancer. DOI: 10.1038/nrc.2016.108	2017	5.61	2020	2022	

Abbreviations: GDS, gene delivery systems; LC, lung cancer.

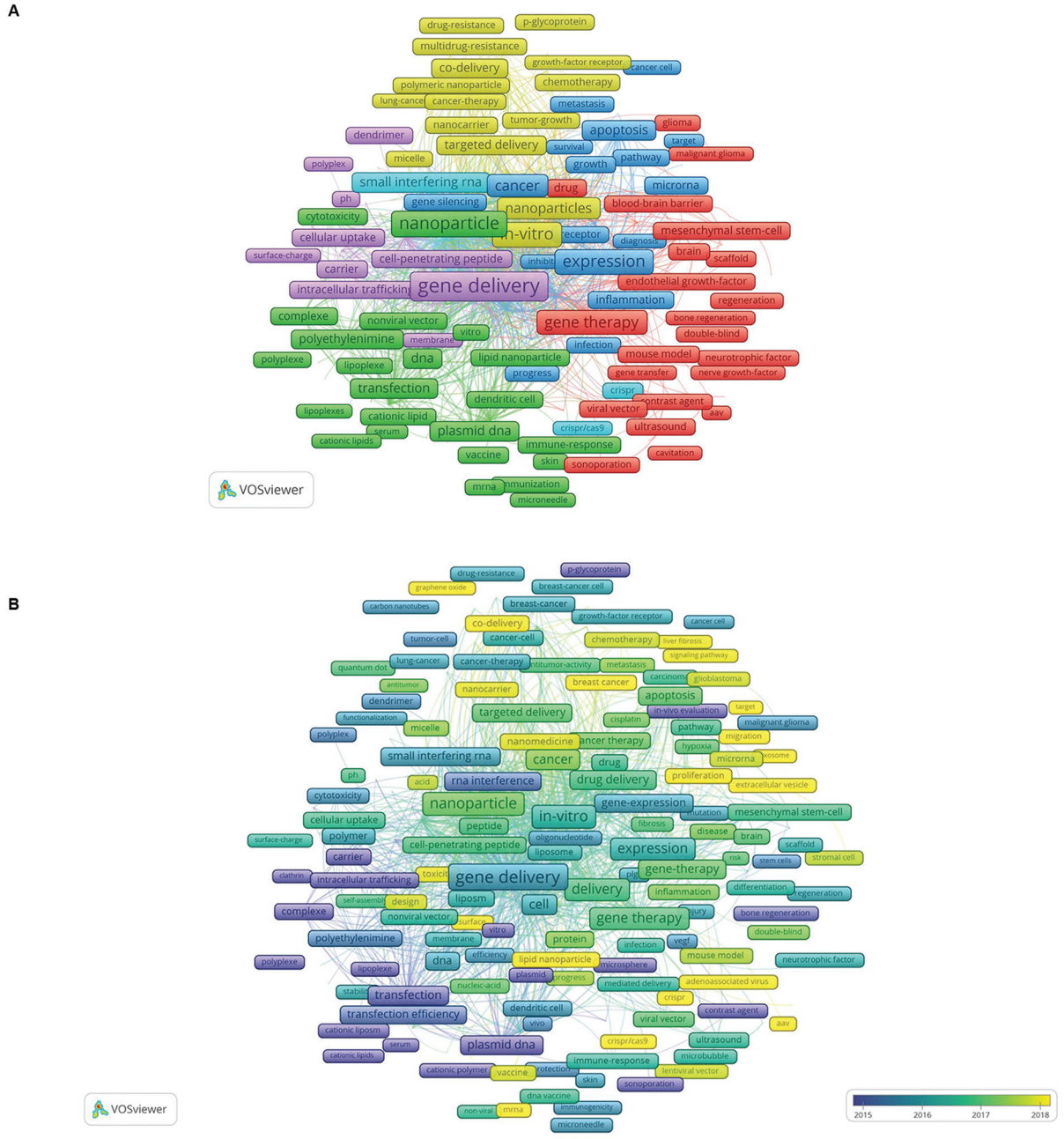


Fig. 12 Keywords regarding GDS for LC. (**A**) Visualization of keyword networks and (**B**) network map depicting keyword relationships, which were generated by VOSviewer. Purple nodes represent earlier keywords, and yellow nodes represent the most recent keywords. The enclosed region has been magnified to provide a more detailed view of the local area. LC, lung cancer; GDS, gene delivery system.

with a minimum frequency of occurrence set at 10. ►**Fig. 12B** displays the overlay visualization of author keywords, where earlier keywords are shown in blue and the most recent keywords are shown in orange. For example, keywords such as "complex," "transfection," and "RNA interference" were the main topics in the early years. The keywords such as "extracellular vesicles," "proliferation," "CRISPR/Cas9," "extracellular vesicle," "co-deliver," and "resistance" remained hot topics recently.

R-Bibliometrix was used to conduct a keyword tree map analysis to visualize the 50 most frequently occurring keywords over time. As shown in ►**Fig. 13**, each cell represented the total frequency of occurrence of a keyword between 2010 and 2022 with the most frequent appearance being "gene delivery" ($n = 329$). ►**Fig. 14** displays the three-factor analysis of the correlation between authors' affiliated organizations (left), keywords (middle), and countries (right). The data showed that ten countries (United States, China, Iran, Korea, Japan, India, Spain, United Kingdom, Canada, and France) published gene therapy-related literature mainly using 10 keywords (gene delivery, gene therapy, nanoparticles, drug delivery, siRNA, siRNA delivery, nanomedicine, cancer, and liposomes).

Trend topic analysis was a vital mapping tool that helped to portray the seed of trend integration rooted in the previous stream. The trend topic map was created using R-Bibliometrix, considering the occurrence frequency of author keywords. The parameters used were a minimum word frequency of 5 and a maximum of 3 words per year. As shown in ►**Fig. 15A**, the duration of "T-cell" was the longest (8 years), followed by "stem cells," "cancer," "gene delivery," and "expression" (7 years). The "exosomes" began to appear in the field of GDS for LC in 2021, and "extracellular vesicles" and "ultrasound" began to appear in the field in 2019. The "T-cell" had the maximum frequency in 2022; nevertheless, "cell-penetrating peptide," "ultrasound," and "extracellular vesicles" had the maximum frequencies in 2021.

The thematic map of keywords was generated using R-Bibliometrix (►**Fig. 15B**). A total of 400 keywords were analyzed, with the lowest cluster frequency of 5, and each cluster had 6 labels. The upper right quadrant (motor theme), which exhibited high density and centrality, likely represented the well-developed and significant themes that contribute to the structure of the GDS for the research field of LC. The cluster included "expression," "nanoparticles," "delivery," "therapy," "cells," and "gene." The upper-left quadrant (niche themes) contained a cluster that included "macular degeneration" and "sustained release." The cluster in the third quadrant (emerging or declining theme) exhibited low centrality and density, indicating its weak development and marginal nature, including "mesenchymal stem cells," "endothelial growth factor," "double blind," "phase I," "bone marrow," and "marrow stromal cells." The fourth quadrant (basic themes) included "*in vivo*," "drug delivery,"

Fig. 13 The keywords plus tree map generated by R-Bibliometrix.

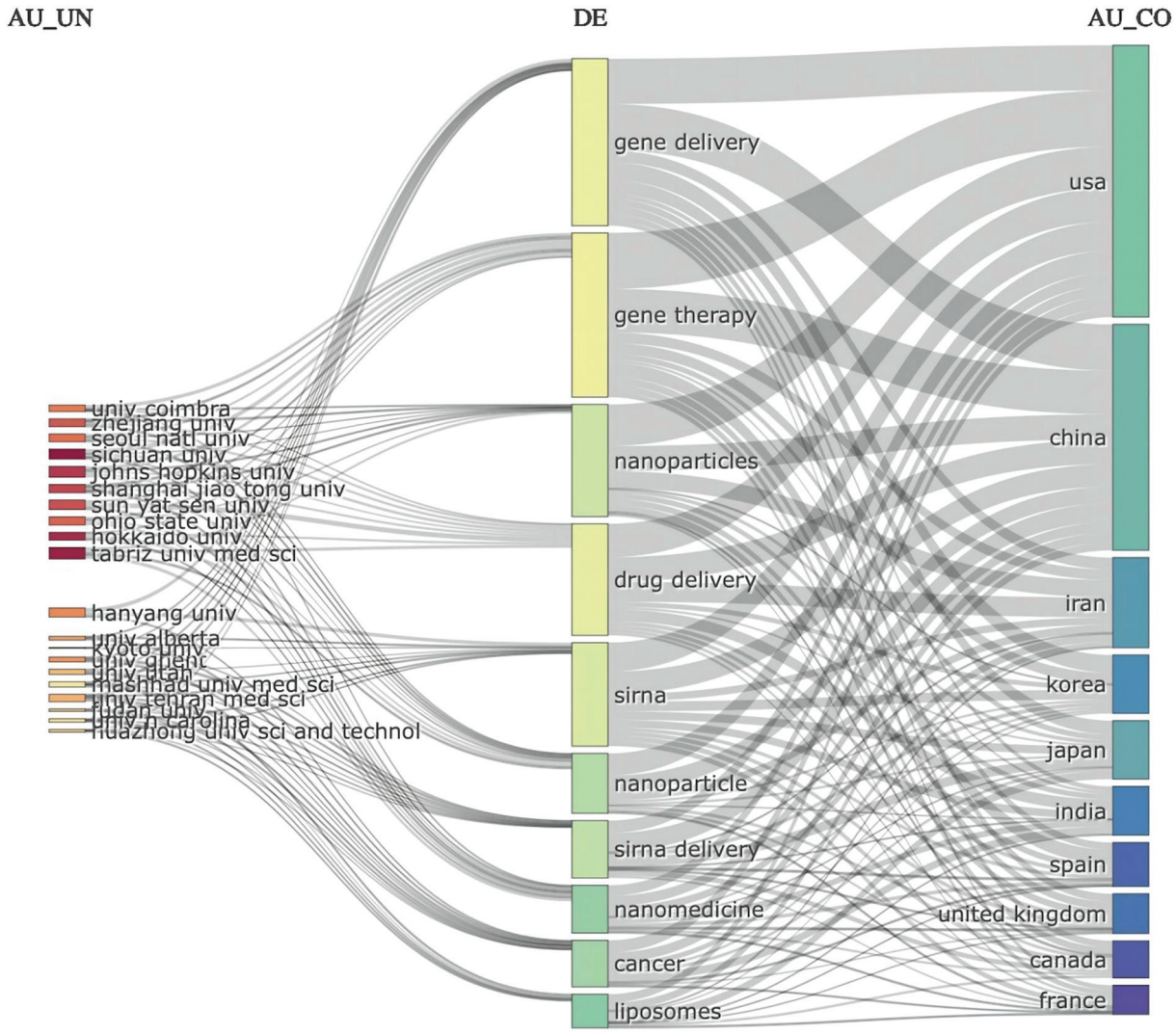


Fig. 14 Three-factor analysis of the relationship among authors' affiliated organizations (left), keywords (middle), and countries (right).

"gemcitabine," "plasmid DNA," and "siRNA delivery." These were cross-cutting themes that cut across different areas of research within the field.

Hotspots and Frontiers in the Field

Several key areas of current research and potential future directions have been delineated through a comprehensive analysis of GDS for LC, drawing upon insights based on analyses of key co-occurrence and trend themes. The identification of major research directions and the evolution of thematic structures in GDS for LC led us to three pivotal areas: T-cell therapy, DNA vaccine development, and the exploration of LC cell-derived exosomes (LCCDEs).

The continued focus on T-cell therapy, especially CAR-T cells, and T-cell receptors (TCRs), from 2014 to 2022 highlighted its importance as a transformative treatment for LC. Despite the potential for off-the-shelf applications and the versatility of TCRs, CAR-T cells still present challenges such as limited antigen coverage, toxicity, low affinity, and major histocompatibility complex restriction. Thus, future research should focus on improving the specificity and safety of T-cell therapies, possibly through the use of novel engineering techniques or the integration of more targeted delivery systems.

At the same time, DNA vaccines, characterized by the stability and efficacy of plasmid DNA, are receiving increasing attention, marking a significant shift in the GDS of the LC (►**Fig. 15A**). Advances in nanotechnology are needed to face the challenges of enzymatic degradation and inefficient cellular uptake of DNA vaccines,[14] and the areas to be explored were liposomes, self-assembling peptides,[15] and electrostatic nanocomplexes for improved delivery mechanisms (►**Fig. 15B**). Future research should optimize these delivery systems to ensure the stability and delivery efficiency of DNA vaccines for more personalized and effective LC therapies.[16]

The growing interest in LCCDEs has opened a new avenue for LC research (►**Fig. 15A**). The dual role of exosomes in gene and protein exchange and cancer progression highlights the complexity of their application in therapy. Future research should aim to understand and utilize the therapeutic and

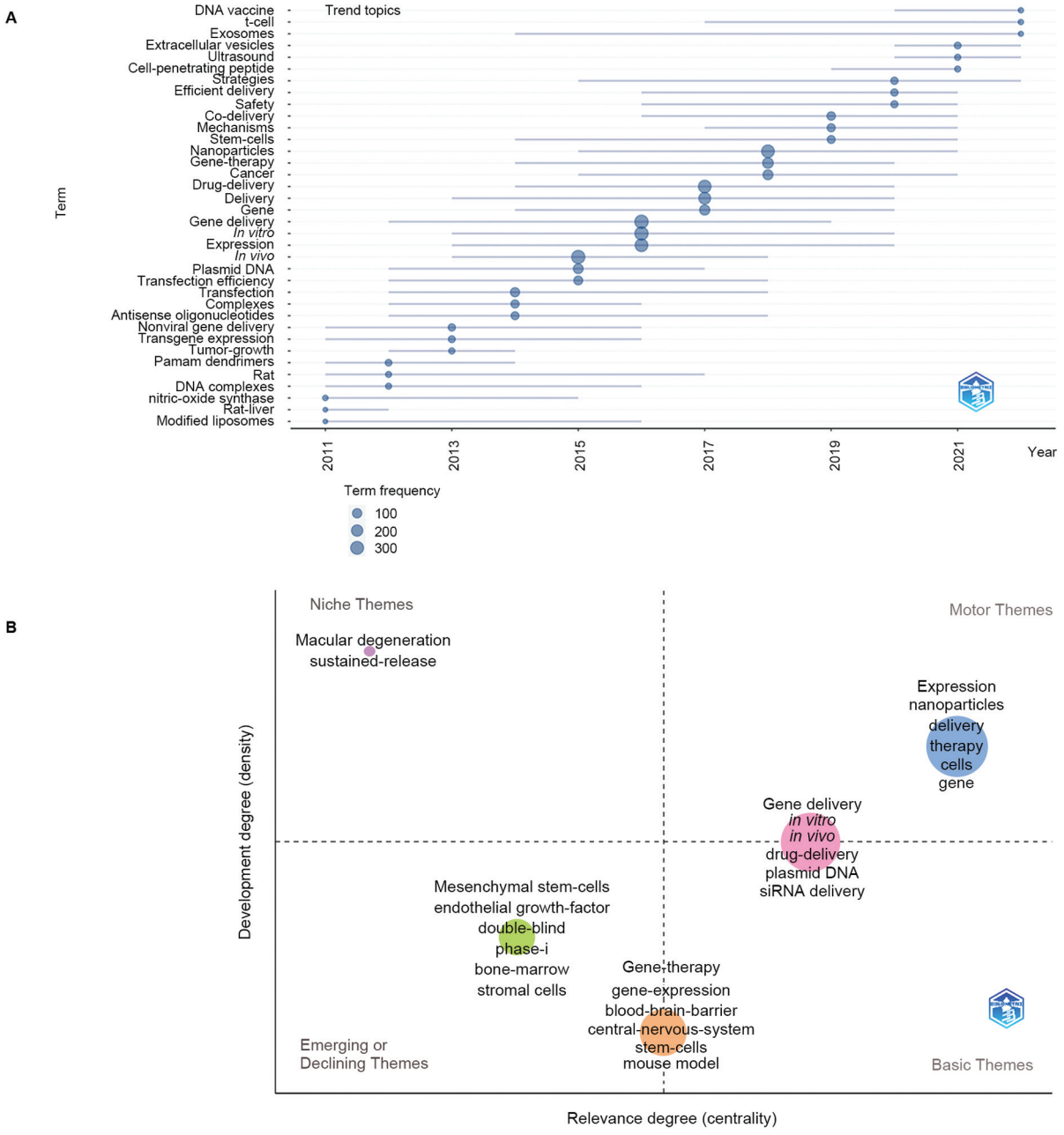


Fig. 15 Trend topic analysis regarding GDS for LC. (**A**) Trending topics. The horizontal axis represents the years, and the vertical axis represents the cumulative occurrences of the keywords. (**B**) Thematic map of keywords generated by R-Bibliometrix. The horizontal axis represents centrality, which indicates the importance of a theme. The vertical axis represents density, which signifies the development of a theme.

diagnostic potential of LCCDEs,[17] while carefully considering their impact on cancer progression.[18]

In summary, the dynamic and multifaceted nature of GDS research targeting LC is highlighted. While promising progress has been made in T cell therapies, DNA vaccine, and exosome research, significant challenges remain. Addressing these challenges requires concerted research and development efforts focused on improving specificity, safety, and delivery mechanisms. The integration of interdisciplinary approaches and innovative technologies is crucial to advancing these frontiers and has the potential to change the landscape of LC therapy.

Advantages and Disadvantages of the Analysis

Our approach is comprehensive, including bibliometric analysis and a review of current research trends. This approach not only provides a holistic view of the evolution of the field and the interconnections of various research efforts, but also serves as an effective investigation for bibliometric analysis of gene delivery studies in LC. To thoroughly capture the current state of GDS research for LC, we used three visualization tools to identify focal points and collaborations among authors, countries, and institutions. Additionally, the database used in our analysis was extensive enough to adequately reflect the current state of gene therapy and gene delivery research in LC.

However, the analysis is limited by a reliance on published literature that may not fully capture ongoing unpublished research or the nuanced challenges encountered by researchers. The focus on high-impact journals and institutions may overlook the significant contributions of smaller research entities. The data were retrieved exclusively from the Web of Science, which consists mainly of research articles and reviews, and therefore may exclude important studies from other databases. In addition, most of the studies included were in English, thus, excluding relevant articles in other languages. Finally, only publications from 2010 to 2022 were included; there is a risk that landmark studies conducted before 2010 may have been omitted, potentially missing foundational evidence in the field.

Conclusion

In this review, the significant advances over the past decade in the field of GDS for LC were highlighted, reflecting the growing research interest in this field. The findings suggest that global interests in diverse approaches to addressing the challenges of gene therapy for LC, as well as collaborations between research institutions, are critical to advancing the field by facilitating the exchange of ideas and technologies across borders. The prominent positions of the Journal of Controlled Release and PNAS in the publishing landscape indicated their influence on GDS for LC and the dissemination of innovative findings. The results of keyword analysis showed the hotspots in GDS for LC, highlighting the shift towards exploring novel delivery mechanisms, understanding resistance pathways in cancer cells, and exploiting extracellular vesicles for therapeutic purposes. This comprehensive review not only summarizes the current state of GDS research for LC, but also provides critical insights into the dynamics of this field from a bibliometric perspective. These insights will be invaluable to researchers in guiding future studies, helping them to identify the most promising areas for breakthroughs in gene therapy for LC.

Data Availability Statement

The original contributions presented in the study were included in the article, and further inquiries can be directed to the corresponding author.

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Conflict of Interest

None declared.

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