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Research article

Current status and future of cancer vaccines: A bibliographic study

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ABSTRACT

Background: Cancer vaccines are an important component of tumour immunotherapy. An increasing number of studies have shown that cancer vaccines have considerable clinical benefits. With the development of tumour precision medicine, cancer vaccines have become important because of their individualised targeting effects. However, few bibliometric studies have conducted comprehensive systematic reviews in this field. This study aimed to assess the scientific output and trends in cancer vaccine research from a global perspective.

Methods: We collected publications on cancer vaccines from the Web of Science Core Collection database, which was limited to articles and reviews in English. Microsoft Excel, VOS Viewer, and CiteSpace V were used for quantitative and visual analyses.

Results: A total of 7807 articles were included. From 1991 to 2022, the number of publications increased annually. The United States had the highest number of articles published in this field (48.28 %), the highest citation frequency (183,964 times), and the highest H-index (182). The National Institutes of Health topped the list with 476 articles. Schlom J had the highest number of published articles (128) and was the main investigator in this field. The journal, Cancer Immunology Immunotherapy, had published the highest number of articles in related fields. In recent years, tumour microenvironment, immune checkpoint inhibitors, particle vaccines, tumour antigens, and dendritic cells have become research hotspots related to cancer vaccines.

Conclusion: Cancer vaccines are a popular research topic in the field of tumour immunotherapy. Related research and publications will enter a boom stage. "Immune checkpoint inhibitors", "tumour microenvironment" and "dendritic cells" may become future research hotspots, while "T-cell suppressor" is a potential puzzle to be solved.

1. Introduction

On 23 February 2023, Merck Sharp & Dohme (MSD) announced that its mRNA cancer vaccine MRNA-4157/V940 combined with pembrolizumab had been granted a breakthrough therapy designation by the U.S. Food and Drug Administration (FDA) for adjuvant therapy in patients with high-risk melanoma after complete resection. This has led to an explosion in cancer vaccine development.

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Research on cancer vaccines has been ongoing for nearly a century but has offered more hope than a clinical impact [1].

Unlike conventional vaccines, cancer vaccines focus on treating rather than preventing disease (except for vaccines against human papillomavirus) [2]. They eliminate cancer cells by activating the immune system to recognise and kill tumour cells [3]. To date, the types of cancer vaccines used in mainstream studies include auto-derived immune cell vaccines, recombinant viral vaccines expressing tumour antigens, peptide vaccines, mRNA vaccines, DNA vaccines, and allogeneic whole-cell vaccines derived from established human tumour cell lines [1,4]. Cancer vaccines approved for clinical use by the FDA include Bacillus Galmette-Guerin (BCG, bacterial-based), Talimogene laherparepvec (TVEC, virus-based), and Provenge (Sipuleucel T, Dendritic cellbased) [5]. Although there have been many encouraging preclinical results for therapeutic cancer vaccines, clinical translation results are not ideal. The reasons for this failure are generally associated with immunosuppression of the tumour microenvironment (TME), lack of a robust T-cell response, vaccine formulation, in vivo delivery of the vaccine, adjuvants, and tumour type [6–9]. In recent years, several scholars have published relevant articles on the principles, development, and clinical research of cancer vaccines. In our previous search, we found a few articles that systematically investigated scientific output and research progress related to cancer vaccines worldwide.

In this study, we conducted a bibliometric analysis to systematically review studies on cancer vaccines. We combined statistical methods with data visualization to analyse the bibliography of relevant literature to identify global research trends and hotspots in the field.

2. Materials and methods

2.1. Data retrieval and literature screening

This study used the Web of Science Core Collection (WoSCC) database expanded by the Science Citation Index (SCI) as the data source. The following search strategies were used for the search:(TS=(“Neoplasms”or “Tumor”or “Neoplasm”or “Tumours”or “Neoplasia”or “Neoplasias”or “Cancer”or “Cancers”or “Malignant Neoplasm”or “Malignancy”or “Malignancies”or “Malignant Neoplasms”or “Neoplasm, Malignant”or “Neoplasms, Malignant”or “Benign Neoplasms”or “Benign Neoplasm”or “Neoplasms, Benign”or “Neoplasm, Benign”))and(TS=(“vaccine”)) not(TS=(“COVID-19″or “COVID 19″or “2019-nCoV Infection”or “2019 nCoV Infection”or “2019-nCoV Infections”or “Infection, 2019-nCoV″or “SARS-CoV-2 Infection”or “Infection, SARS-CoV-2″or “SARS CoV 2 Infection”or “SARS-CoV-2 Infections”or “2019 Novel Coronavirus Disease”or “2019 Novel Coronavirus Infection”or “COVID-19 Virus Infection”or “COVID 19 Virus Infection”or “COVID-19 Virus Infections”or “Infection, COVID-19 Virus”or “Virus Infection, COVID-19″or “COVID19″or “Coronavirus Disease 2019″or “Disease 2019, Coronavirus”or “Coronavirus Disease-19″or “Coronavirus Disease 19″or “Severe Acute Respiratory Syndrome Coronavirus 2 Infection”or “COVID-19 Virus Disease”or “COVID 19 Virus Disease”or “COVID-19 Virus Diseases”or “Disease, COVID-19 Virus”or “Virus Disease, COVID-19″or “SARS Coronavirus 2 Infection”or “2019-nCoV Disease”or “2019 nCoV Disease”or “2019-nCoV Diseases”or “Disease, 2019-nCoV″or”COVID-19 Pandemic”or “COVID 19 Pandemic”or“Pandemic, COVID-19″or“COVID-19 Pandemics”)) not(TS=(“Influenza, Human”or “Human Influenzas”or “Influenzas, Human”or “Influenza”or “Influenzas”or “Human Flu”or “Flu, Human”or “Human Influenza”or “Influenza in Humans”or “Influenza in Human”or “Grippe”))and (WC=(Oncology)). The period was from database establishment to 17 January 2023. The search was limited to articles in English. For manuscript types, we included original articles and reviews and eliminated all other sources to ensure research quality (Fig. 1).

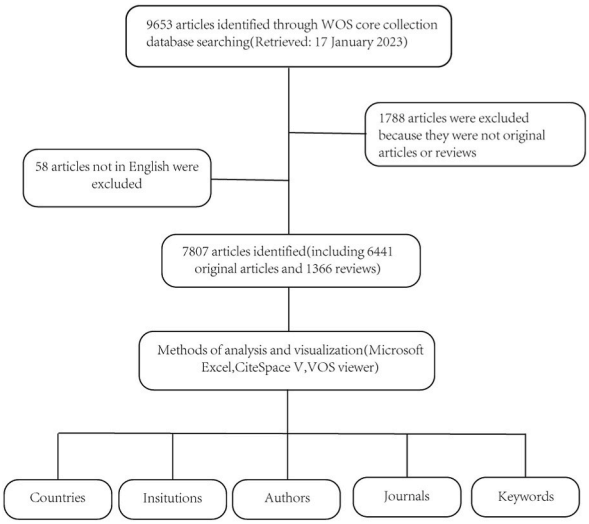

Fig. 1. Flowchart of the selection of publications included in this study.

2.2. Data extraction and analysis

Data were extracted independently by two authors, including annual publication volumes, countries, institutions, authors, journals, citations and keywords. We used Microsoft Excel 2021 for the quantitative analysis to calculate the total number of published articles over the years, the average number of citations for each article, the number of papers published in each country over the years, the cumulative number of published papers, and the cumulative number of papers published by various institutions, authors, and journals. As an evaluation indicator of publications, we mainly used Impact Factor (IF) and category data from Journal Citation Reports (JCR) published in 2022 to evaluate the quality of scientific information. The H-index is also used to assess the amount and level of academic output of researchers, and the productivity and industry influence of countries, institutions, and journals. H represents highly cited papers, and a researcher's H-index indicates that most H papers have been cited at least H times.

For the visualised analyses, we used VOS viewer (version 5.8. R3) for cooperation and co-citation analyses among countries, institutions, authors, journals, and co-occurrence analyses of keywords. CiteSpace V (version 6.1. R6) was used to create a dual-map overlay of journals and generate powerful keywords and citation lists. Each node in the diagram represents a different parameter, including countries, institutions, and keywords. The weighting of the parameters determines the size ratio of the node, such as the number of publications, number of citations, or frequency of occurrence. The higher the weight, the larger the node. Nodes and lines are coloured according to the cluster to which they belong. The lines between nodes represent the links. Total link strength (TLS) represents the strength of the cooperative or co-citation link between countries, institutions, and authors.

2.3. Research ethics

Ethical approval was not required for our study as the data used were downloaded from public databases, and it did not involve any human or animal studies.

3. Results

3.1. Publication outputs and citation trend

In total, 7807 articles on cancer vaccines were retrieved from the WOSCC database up to 17 January 2022, including 6441 original articles and 1366 reviews. The number of publications has increased annually since 1991 and has remained particularly high in the previous three years (Fig. 2). According to the search results, the total citation frequency of the included studies was 296,185 and the average citation frequency of each literature was 37.94 times. The H-index of this academic field during this period was 197, indicating that this field had a high academic level, and academic output had research value and prospects.

3.2. Distribution of countries

Table 1 shows the top 10 countries with the highest number of publications related to cancer vaccines, whereas Fig. 3A shows the cumulative trend of publications from 1947 to 2023. In summary, the number of publications in the United States was the largest among the included studies, accounting for 48.28 % (3769/7808), followed by China (12.95 %, 1011/7808), and Japan (8.94 %, 698/7808). Publications from the United States had the highest number of citations (183,964) and H-index (182). Owing to collaboration between authors from different countries, the total number of articles from each country overlapped (>100 %). Fig. 3B shows the bibliographic references of these countries. The United States had the largest TLS (29,045), followed by Germany (25,698) and France (21,903).

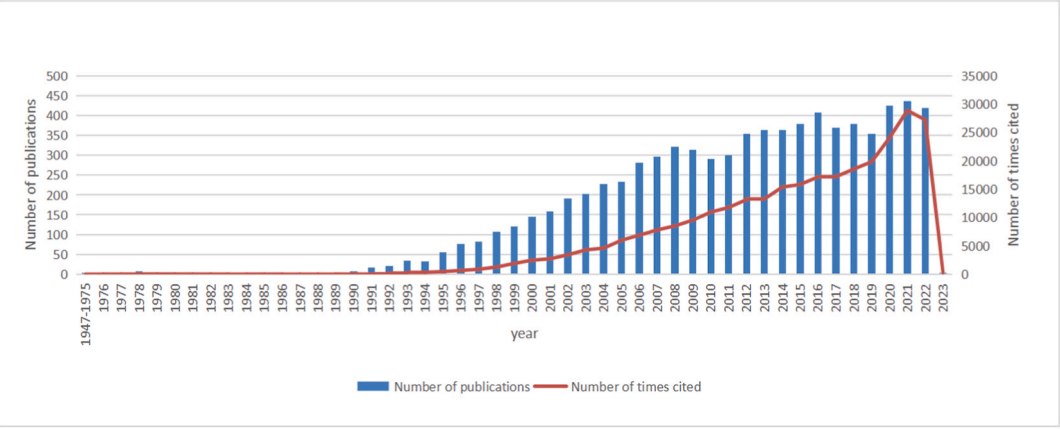

Fig. 2. Trend of the number of articles published annually and the total number of citations of articles annually.

Table 1
The top 10 productive countries with publications.

Rank	Country	Article count	Percentage(n/7807)	H-index	TLS	Total citations	Average citation per article
1	USA	3769	48.28	182	29045	183964	48.81
2	CHINA	1011	12.95	59	7151	20999	20.77
3	JAPAN	698	8.94	62	4771	18913	27.1
4	GERMANY	588	7.53	83	7400	25698	43.7
5	ITALY	426	5.46	62	5475	16502	38.74
6	ENGLAND	401	5.14	74	5710	19564	48.79
7	FRANCE	341	4.37	77	6323	21903	64.23
8	NETHERLANDS	330	4.23	78	5981	19612	59.43
9	CANADA	277	3.55	63	4662	15846	57.21
10	BELGIUM	210	2.69	61	4837	12837	61.13

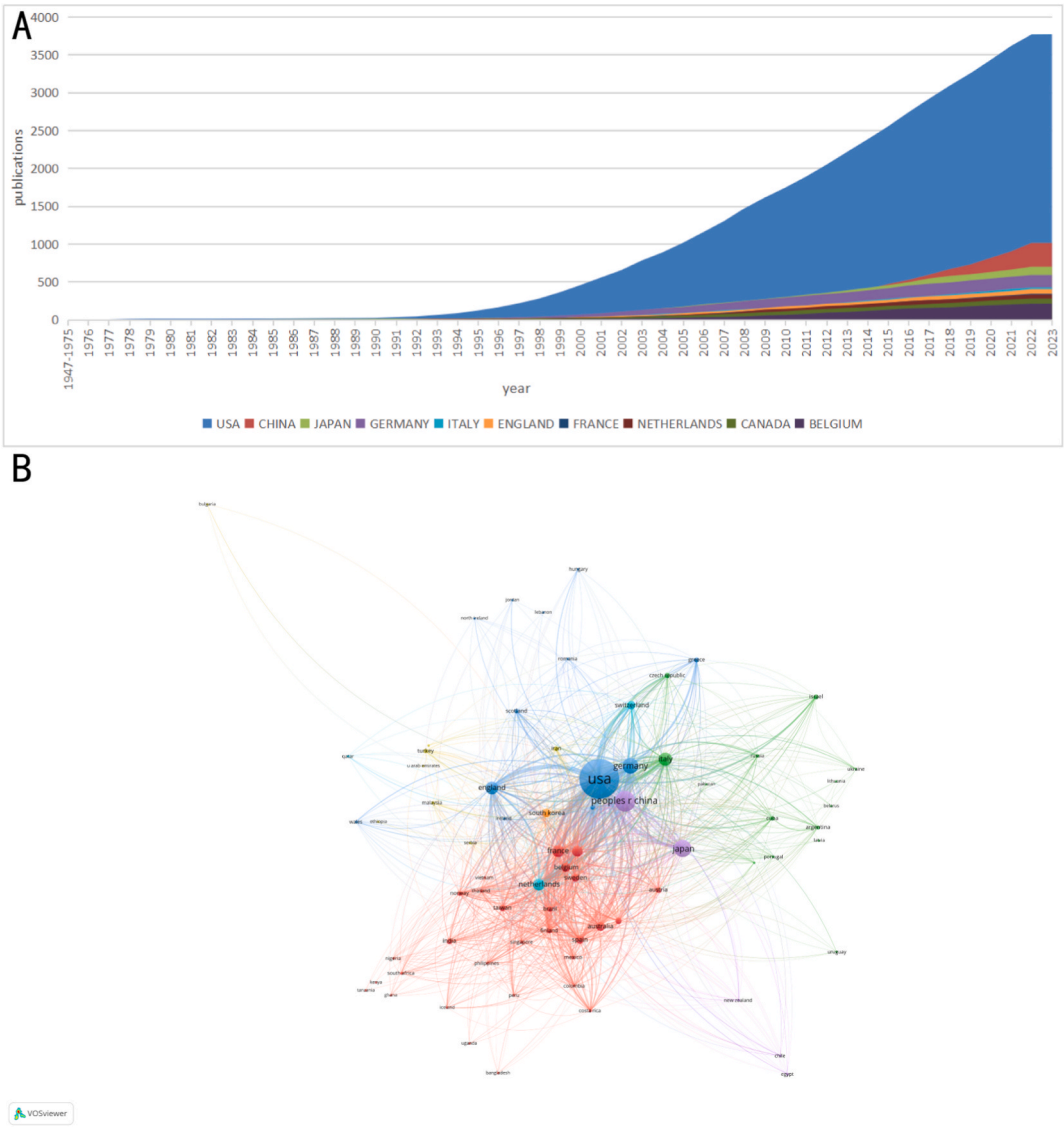

Fig. 3. A. Trend of the annual number of publications in the top 10 countries. B. Country citation network visualization map generated by VOS viewer software.

3.3. Distribution of institutions

A total of 5612 institutions published articles on cancer vaccines. Table 2 lists the top 10 institutions in terms of the number of articles published. Most of the agencies were affiliated with the United States, with only one from Germany. The National Institutes of Health contributed the highest number of publications (476), followed by the National Cancer Institute (439), and the University of Texas System (284). The National Institutes of Health had the highest H-index and Johns Hopkins University had the highest number of citations per article.

Fig. 4A and B shows the cooperation and citation networks between institutions using VOS viewer (version 5.8. R3). As shown in Fig. 4A, there were 809 items and 9489 links on the map. The 809 items were grouped into 17 colour-coded clusters, meaning that the institutions in each cluster worked closely together. Fig. 4B shows a network map of the institutions' citations, which contained 809 items and 58,035 links. The institution with the largest TLS was the National Cancer Institute (10,221). Only institutions that published more than five relevant articles are shown in the figure.

3.4. Authors and Co-cited authors

A total of 33,720 authors participated in this study. Table 3 lists the 10 authors with the highest number of publications in this field. Schlom J, affiliated with the National Institutes of Health, published the highest number of articles (128) and had the highest H-index (59). Jaffee EM of Johns Hopkins University in the United States had the highest number of citations per article (93.56 times per article).

Fig. 5A shows the collaboration network among authors with more possibilities for collaboration among authors in the same country or institution. Prolific authors, such as Schlom J and Itoh K had active and dense networks of collaborators. Fig. 5B shows the co-citation network between the authors, which included 288 items, 9 clusters, and 8691 links. The top three authors with the greatest TLS were Schlom J (TLS = 3165), Gulley JL (TLS = 2862), and Itoh K (TLS = 2161). Owing to the number limit, only authors who have published more than 10 relevant articles are shown in the figure.

3.5. Journals and Co-cited journals

A total of 303 journals had published articles on cancer vaccines. We listed the top 10 journals using a comprehensive quality assessment (Table 4). As shown in the table, the top 10 journals published 3280 articles, accounting for 42.0 % of the included articles, indicating that these journals occupied an important position in the field. *Cancer Immunology Immunotherapy* (IF 2022 = 6.63) published the highest number of articles(743), followed by *Clinical Cancer Research* (IF 2022 = 13.801, count: 435) and *International Journal Of Cancer* (IF 2022 = 7.316, count: 395). Of the top 10 journals, six were from the US, two from Switzerland, one from the UK, and one from Greece. Among the top 10 journals, eight were high-quality SCI Q1 journals. *Clinical Cancer Research* had the highest H-index (96) and IF (IF 2022 = 13.801) in this field. *Cancer Research* had the highest number of citations (33,468).

Fig. 6 shows a dual-map overlay of relevant journals, revealing the citation relationships of journals in this field through intuitive visualization. The labels represent the domains to which the journal belongs. The left side of the map represents the field of journals in which the cited literature is located and the right side represents the field of journals in which the cited literature is located. The different colours represent different reference paths. Three major reference paths are identified in the figure: an orange path and two green paths. The orange path indicates the included articles published in journals related to Molecular, Biology, and Immunology and

Table 2
Top 10 institutions ranked by number of publications.

Rank	Institution	Country	Article count	H-index	Total citations	Average citation per article
1	NATIONAL INSTITUTES OF HEALTH NIH USA	United States	476	92	30545	64.17
2	NATIONAL CANCER INSTITUTE NCI	United States	439	90	29036	66.14
3	UNIVERSITY OF TEXAS SYSTEM	United States	284	59	12070	42.5
4	JOHNS HOPKINS UNIVERSITY	United States	263	76	22388	85.13
5	UNIVERSITY OF CALIFORNIA SYSTEM	United States	254	61	13392	52.72
6	HARVARD UNIVERSITY	United States	239	62	13050	54.6
7	UTMD ANDERSON CANCER CENTER	United States	224	54	10361	46.25
8	MEMORIAL SLOAN KETTERING CANCER CENTER	United States	196	62	12158	62.03
9	PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION PCSHE	United States	193	57	11428	59.21
10	HELMHOLTZ ASSOCIATION	Germany	179	46	7262	40.57

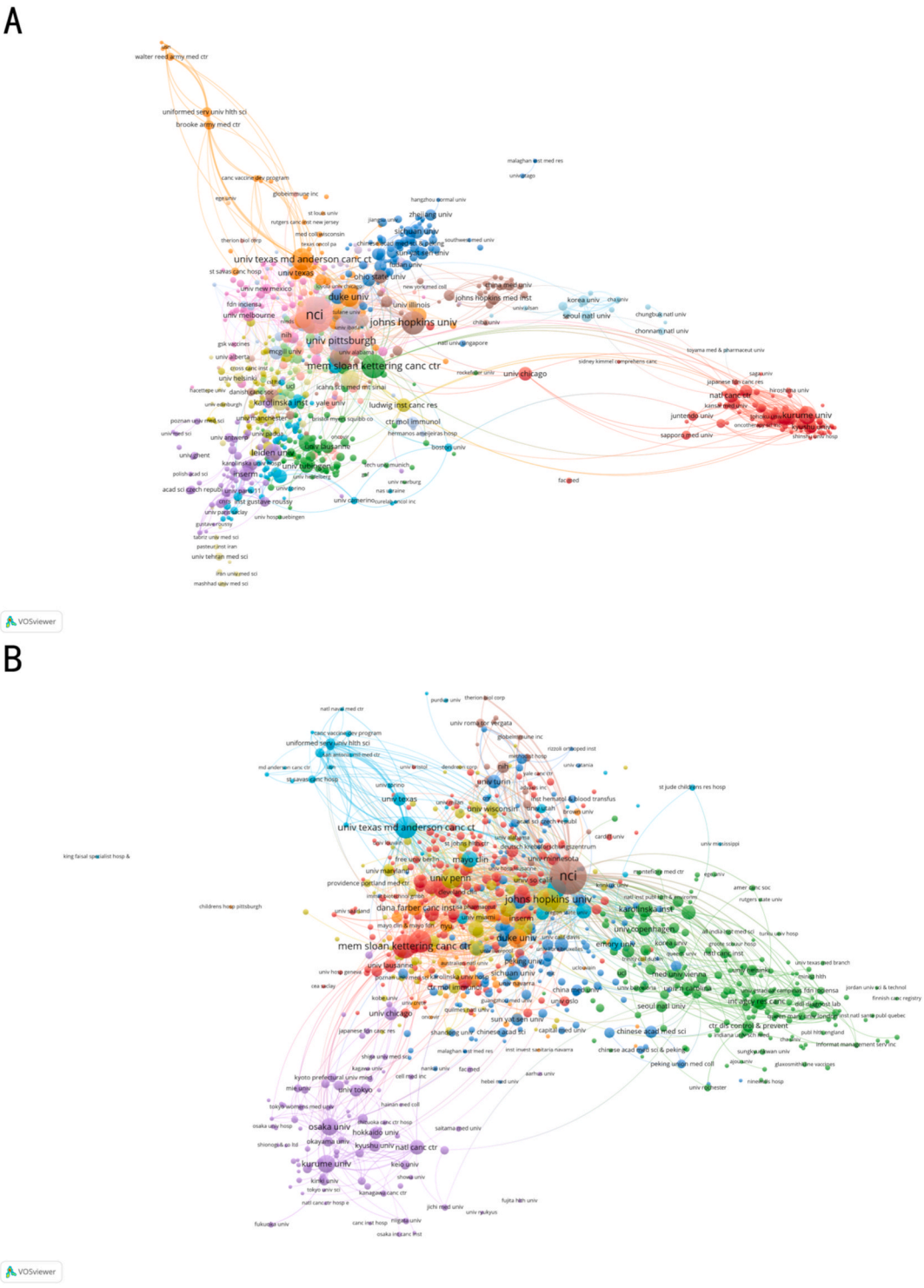

Fig. 4. A. Institutions' collaboration network visualization map generated by VOS viewer software. B. Institutions' citation network visualization map generated by VOS viewer software.

cited articles published in journals related to Molecular, Biology, Genetics. Green paths show articles published in journals related to Medicine, Clinical and cited articles published in journals related to Molecular, Biology, Genetics and Health, Nursing, Medicine. The determination of the citation path can indicate the causal relationship between literature and journal. The cited literature (on the left side of the map) can be regarded as applied research, whereas the cited literature (on the right side of the map) can be regarded as basic

Table 3
Top 10 most productive authors in terms of number of publications.

Rank	Author	Article count	H-index	Country	Total citations	Average citation per article	Institution
1	Schlom J	128	59	United States	9412	73.53	National Institutes of Health (NIH)
2	Itoh K	87	28	Japan	2079	23.9	Kurume University
3	Gulley JL	71	31	United States	4020	56.62	National Institutes of Health (NIH)
4	Hodge JW	59	36	United States	4679	79.31	National Institutes of Health (NIH)
5	Yamada A	57	25	Japan	1449	25.42	Tokyo Institute of Technology
6	Slingluff CL	55	27	United States	2262	41.13	University of Virginia
7	Jaffee EM	54	32	United States	5053	93.56	Johns Hopkins University
8	Van Der Burg SH	53	31	Netherlands	3940	74.34	Leiden University Medical Center (LUMC)
9	Disis ML	49	25	United States	3706	75.63	University of Washington Seattle
10	Peoples GE	49	29	United States	2244	45.8	Uniformed Services University of the Health Sciences

research.

3.6. Citations and Co-cited citations

We counted the top 10 articles with the highest number of citations in the field of cancer vaccines (Table 5). As shown in the table, there were several journals in this field with profound academic output, and the top 10 articles were cited more than 800 times. The study by Liu et al.(2018), published in *Oncotarget*, was the most cited article at 1524 times. CiteSpace V (version 6.1R6) was used to analyse the citation frequency of the articles. Fig. 7A shows the 25 references that burst over time. The citation burst first appeared in 1998 and was the result of an article published that year. More than half of the citation bursts occurred between 2008 and 2016. The latest burst of citations occurred in 2019 and is ongoing.

3.7. Keywords analysis of research hotspots

We extracted keywords from the titles and abstracts of 7807 articles for analysis. Keywords that appeared more than 100 times were used to generate a visualization map using the VOS viewer. The map contained 131 keywords (Fig. 8A). Cluster analysis was then conducted on these high-frequency keywords, and four clusters were obtained (Cluster 1: Red, Cluster 2: Green, Cluster 3: Yellow; Cluster 4: Blue).

As shown in the figure, Cluster 1 had the largest range, and the most frequent keywords were immunotherapy (2420 times), vaccine (1595 times), and melanoma (755 times). The main keywords in Cluster 2 were dendritic cells (1385 times), expression (1043 times), and T cells (751 times). The main keywords in Cluster 3 were antigen (670 times), response (610 times), and induction (524 times). The main keywords in Cluster 4 were tumour (1361 times), vaccination (686 times), and cervical cancer (417 times). We then added the time axis to the clustered images (Fig. 8B), and the colour of the keywords changed from blue to yellow over time, indicating that hot spots related to immunity and T-cell expression have appeared in recent years.

Fig. 7B lists the burst keywords for the different phases through CiteSpace V. Keyword bursts reflect the research hotspots and academic frontiers of a certain field. The red part indicates that these keywords show a blowout trend at this stage. We noted that there were still some breakout keywords in the last two years, such as open-label, suppressor cell, immune checkpoint inhibitor, and tumour microenvironment. The findings indicate that these research directions have received significant attention in recent years and may become the focus and direction of future research.

4. Discussion

In this study, we conducted a systematic analysis of the global scientific output related to cancer vaccines from 1947 to 2023 using bibliometric analysis. As shown in Fig. 2, this field had become dormant since the first cancer vaccine-related article was published in 1947 until 1991 when the number of global publications on cancer vaccines began to increase annually. Between 1991 and 2016, the global trend of relevant publications increased and stabilised in recent years. Given that some studies in 2022 have not yet entered the WoSCC database, we can predict that this field will enter the stage of rapid development in the next few years.

At the national level, the United States had the largest scientific output in this field, with far more publications than any other country. Additionally, the United States had the highest H-index, TLS, and number of citations in this field, indicating that the quality of published articles from the United States was high, accounting for half of the articles in this field. China and Japan had the second-largest number of published papers; however, it is worth noting that their H-index and average number of citations were slightly lower

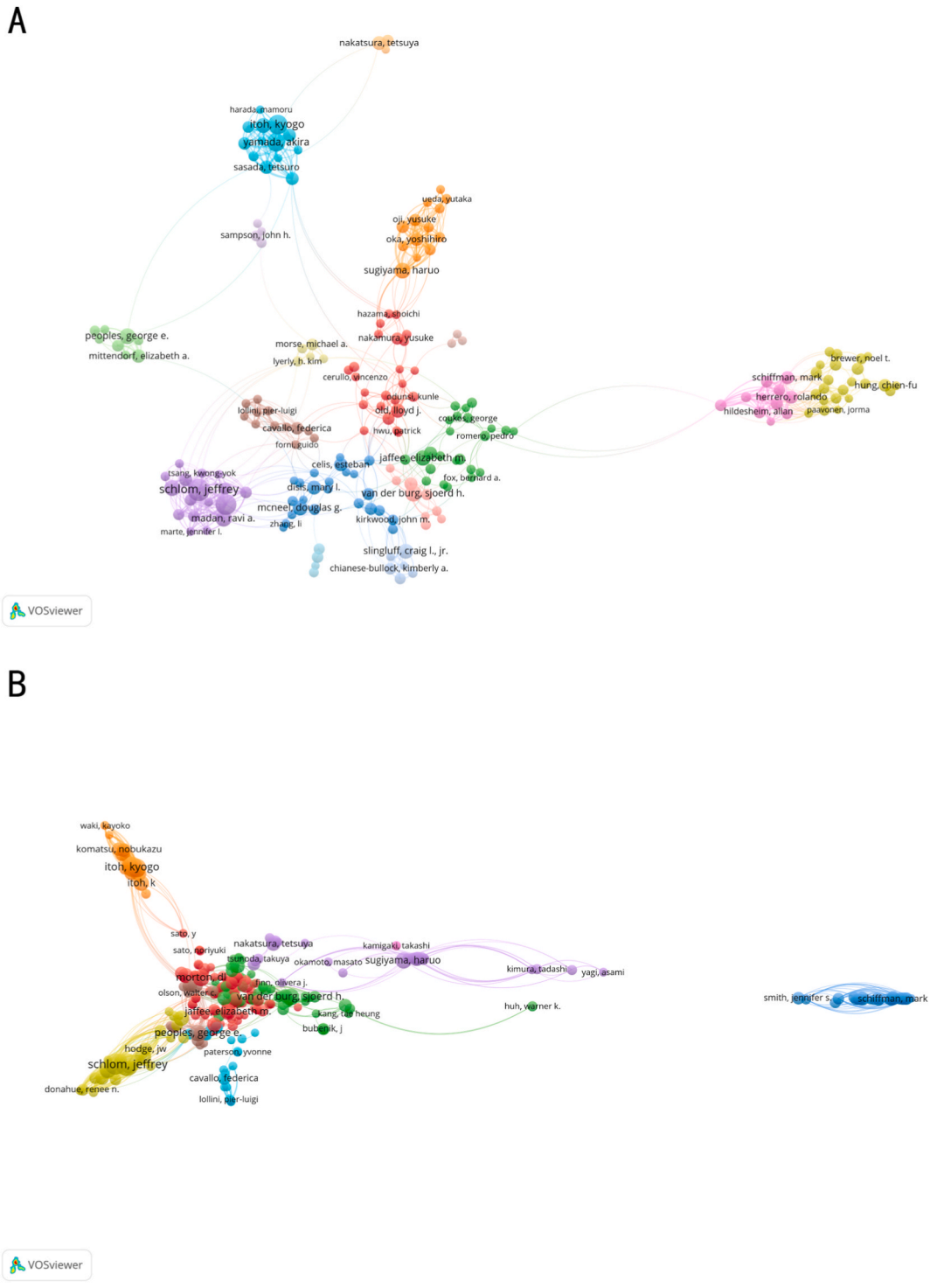

Fig. 5. A. Authors' collaboration network visualization map generated by VOS viewer software. B. Authors' co-citation network visualization map generated by VOS viewer software.

than those of other countries, suggesting that these countries should pay more attention to the quality of published papers.

In our analysis, we found that nine of the top 10 institutions were from the US, and only one was from Germany. This is intrinsically related to the abundant scientific output of the United States in this field. This result indicates that the establishment of first-class universities or scientific research institutions is an important basis for promoting national academic status.

Table 4
Top 10 research journals ranked by number of publications.

Rank	Journal Title	Country	Count	IF (2022)	Quartile in category (2022)	H-index	Total citations
1	CANCER IMMUNOLOGY IMMUNOTHERAPY	United States	743	6.63	Q1	77	25958
2	CLINICAL CANCER RESEARCH	United States	435	13.801	Q1	96	32272
3	INTERNATIONAL JOURNAL OF CANCER	Switzerlands	395	7.316	Q1	68	19607
4	CANCER RESEARCH	United States	391	13.312	Q1	95	33468
5	JOURNAL OF IMMUNOTHERAPY	United States	339	4.912	Q2	63	13792
6	ONCOIMMUNOLOGY	United States	275	7.723	Q1	46	8324
7	CANCERS	Switzerlands	216	6.575	Q1	25	2233
8	JOURNAL FOR IMMUNOTHERAPY OF CANCER	United States	190	12.469	Q1	28	3515
9	CANCER GENE THERAPY	England	157	5.854	Q1	35	4202
10	ANTICANCER RESEARCH	Greece	139	2.435	Q4	27	2361

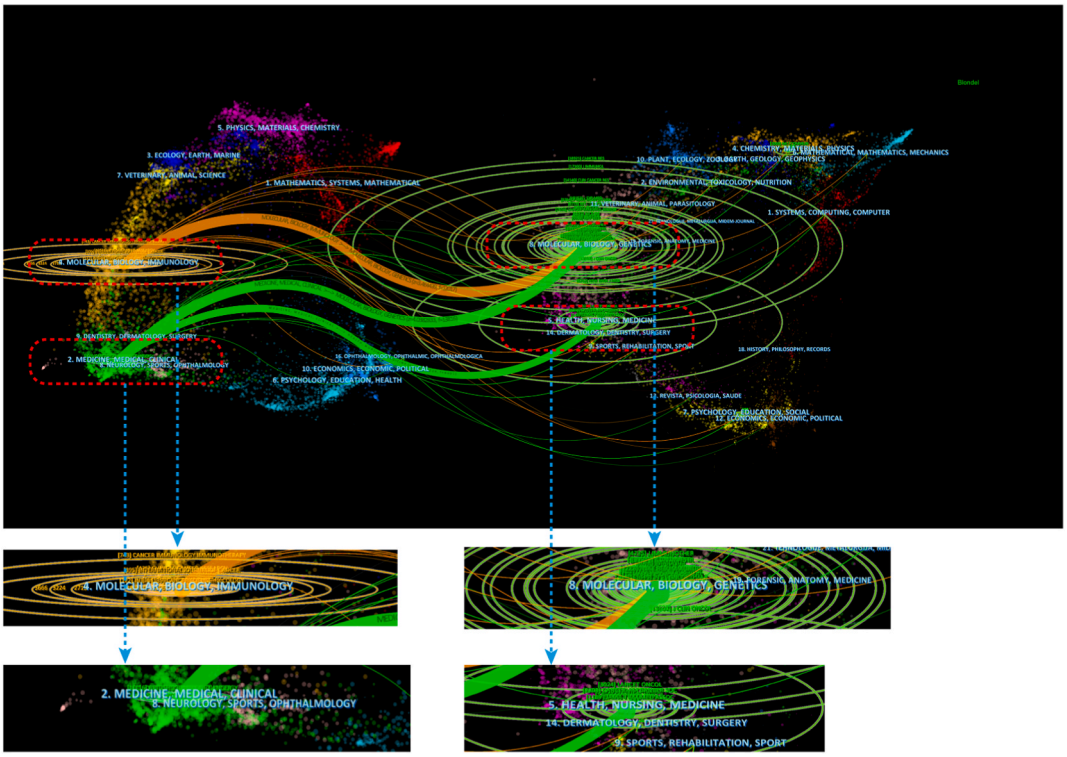

Fig. 6. Dual-map overlay of the relevant journals generated using CiteSpace software.

We also analysed the top 10 authors in this field, including seven from the United States, two from Japan, and one from the Netherlands. Schlom J from the National Institutes of Health was the contributor with the highest number of articles in this area, followed by Itoh K from the University of Kurume and Gulley JL from the National Institutes of Health. Fig. 5A shows a network visualization of the cooperation among authors, which can be used to intuitively understand whether there is cooperation among various authors. Nodes (authors) with the same colour in the figure indicate a cooperative relationship between them. Fig. 5B shows a relationship diagram of the authors' mutual references. Article citation can be regarded as passive cooperation. Nodes (authors) marked with the same colour indicate that they share a similar or common research direction: the larger the node, the higher the status of the author. This analysis can help new researchers understand collaborative relationships and identify important authors in the field. Authors with abundant output in this field, such as Schlom J and Itoh K, all had efficient and close cooperative networks, among which Schlom J had the highest co-citation link strength. These authors and their research teams are likely to publish high-quality articles on cancer vaccines in the future.

In terms of journals, the journals listed in Table 4 accounted for nearly half of the included articles, suggesting that researchers could submit relevant manuscripts to these journals. In the table, eight journals belong to Area 1 of the SCI partition, and their impact factors are all greater than five. Among the top 10 journals, three had impact factors greater than 10: *Clinical Cancer Research* (IF2022, 13.801), *Cancer Research* (IF2022, 13.312), and *Journal for Immunotherapy of Cancer* (IF2022, 12.469). Based on journal quality and number of publications, we believe that *Cancer Immunology Immunotherapy* (IF2022, 6.63), *Clinical Cancer Research* (IF2022, 6.63),

Table 5
Top 10 cancer vaccine-related articles with the highest number of citations (up to 17 January 2023).

Title	First author	Journal	Year	Citations	Main conclusion
Dendritic cells loaded with tumor derived exosomes for cancer immunotherapy	Liu, HY	ONCOTARGET	2018	1524	They summarized the role of Dendrite cells (DCs) loaded with tumor derived exosomes (TEXs) in tumor immunotherapy, suggesting that mature DCs induced by TEXs induced CD8+T cell differentiation and thus enhanced anti-tumor immune function. Exosomes have great potential in tumor immunity. Its strong antigenicity, applicability and convenience of storage and extraction make it a kind of high efficiency antigen. They propose that DC vaccine-loaded exosomes in combination with adjuvants and immune checkpoint inhibitors may be the key to future tumor therapy.
Cancer immunotherapy via dendritic cells	Palucka, K	NATURE REVIEWS CANCER	2012	1390	They made a systematic review of dendritic cells (DCs), and clarified that DC is an important target for anti-tumor immunotherapy from the perspectives of DC biology and the progress of DC vaccination strategy. They propose that DC-based therapy is the frontier of cancer immunotherapy.
Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update	Smith, JS	INTERNATIONAL JOURNAL OF CANCER	2007	1226	This is a meta-analysis of the distribution of HPV types in invasive cervical cancer (ICC) and high-grade squamous intraepithelial lesions (HSIL). A total of 130 ICC and 85 HSIL-related studies were included, including 14595 ICC and 7094 HSIL cases. The study showed that 70 % of ICC cases were associated with HPV16 (55 %) and HPV18 (15 %) infection, and the prevalence of HPV16/18 in HSIL cases was 52 %. Overall, the eight most common HPV types in HSIL were essentially the same as those found in cervical cancer, with the exception of HPV45. This meta-analysis suggests that a prophylactic vaccine against HPV16/18 has the potential to prevent more than two-thirds of ICC cases and half of HSIL cases worldwide.
Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial	Villa, LL	LANCET ONCOLOGY	2005	1147	They evaluated the effectiveness of a prophylactic quadrivalent vaccine in a phase 2 clinical trial. There was a 90 % reduction in persistent infection or clinical illness of HPV6/11/16/18 in the vaccine group compared to the placebo group (95%CI 71–97, $P < 0.0001$). The results showed that the vaccine against HPV type 6/11/16/18 significantly reduced the incidence of infection and disease caused by common HPV types.
Worldwide burden of cancer attributable to HPV by site, country and HPV type	de Martel, C	INTERNATIONAL JOURNAL OF CANCER	2017	917	They assessed the global burden of cancer caused by HPV. Based on GLOBOCAN 2012 data, 4.5 % of cancers worldwide (630,000 new cancer cases per year) can be attributed to HPV. Their results suggest that 70 to 90% of cancers attributed to HPV could be prevented through universal, high coverage of HPV vaccination, with women more protected than men by the vaccine.
The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research	Cheever, MA	CLINICAL CANCER RESEARCH	2009	913	This is a pilot project of the National Cancer Institute's prioritization of cancer antigens to reflect the current state of the cancer vaccine field and to inform decisions on the conversion of the most promising cancer antigens into cancer treatment or preventive vaccines. The antigen ranking of this project was mainly based on "oncogenicity", "specificity" and "stem cell expression", and the results showed that the translocation fusion gene breakpoints (Ewing's sarcoma

(*continued on next page*)

Table 5 (*continued*)

Title	First author	Journal	Year	Citations	Main conclusion
					and alveolar rhabdomyosarcoma; ALK, bcr-abl and ETV6AML) and mutated oncogenes (ras) ranked the highest.
Metronomic cyclophosphamide regimen selectively depletes CD4(+) CD25(+) regulatory T cells and restores T and NK effector functions in end stage cancer patients	Ghiringhelli, F	CANCER IMMUNOLOGY IMMUNOTHERAPY	2007	903	They demonstrated that cyclophosphamide (CTX) rhythm therapy can selectively deplete $CD4^{+}CD25^{+}$ regulatory T cells (Treg) and inhibit tumor angiogenesis, thereby better controlling tumor progression. At the same time, it was also observed that the immune response of tumor patients was restored one month after receiving CTX rhythm therapy, which provided a possibility for the recovery of immune function in patients with end-stage tumor.
Non-small cell lung cancer: current treatment and future advances	Zappa, C	TRANSLATIONAL LUNG CANCER RESEARCH	2016	889	They summarized the current treatment of lung cancer systematically, including risk factors for lung cancer, current treatment strategies, biomarker tests, the role of immunotherapy and immunotherapy via vaccines. They propose that vaccine therapy for non-small cell lung cancer aims to alter the immune balance in favor of activation so that the host responds to antigen-associated antigens. There are currently a number of Phase 3 trials involving potential new vaccine therapies for non-small cell lung cancer.
The Pancreas Cancer Microenvironment	Feig, C	CLINICAL CANCER RESEARCH	2012	869	They reviewed current studies on the microenvironment of Pancreatic ductal adenocarcinoma(PDA). Due to the abundant tumor stromal of PDA supporting tumor growth and promoting metastasis, and acting as a physical barrier of drug delivery, the systematic treatment of PDA is not satisfactory. They suggest that targeting the tumor microenvironment as a promising strategy for the future can be done by reducing the connective tissue interstitium, exploiting a poor vascular system, or activating the immune system to target tumor cells.
Treatment of established tumours with a novel vaccine that enhances major histocompatibility class II presentation of tumor antigen	Lin, KY	CANCER RESEARCH	1996	847	They created a chimera (Sig/E7/LAMP-1) by linking the sorting signal of a lysosome associated membrane protein (LAMP-1) to the cytoplasmic/nuclear human papilloma virus (HPV-16) E7 antigen. It was found that the chimera expressed recombinant vaccinia vector in vivo and in vitro, enhancing the ability of MHC Class II molecules to present to CD4+T cells. At the same time, they demonstrated that redirecting cytoplasmic tumor antigen to endosomal/lysosomal compartments can greatly improve the therapeutic efficacy of recombinant vaccines in vivo.

13.801) and *Cancer Research* (IF2022, 13.312) may be the core journals for published articles in the field of cancer vaccines. It is not hard to see that the quality of the articles on cancer vaccines is reliable, indicating that high-quality research in this area is in full swing.

"Reference with strongest citation bursts" means that a study is frequently cited in a period of time. This indicates that this study has attracted extensive attention in academic circles during this period and can reflect dynamic changes in the direction and hotspots of cancer vaccines over time. The first citation burst started in 1998 and continued through 2003, and stemmed from the study by Steven A. Rosenberg et al., in 1998. In another study [10], they evaluated a synthetic peptide vaccine for melanoma and proposed a novel cancer immunotherapy based on a synthetic peptide vaccine encoding a cancer antigen gene. The first citation burst attracted the attention of scholars in fields related to the clinical application of cancer vaccines.

Approximately half of the citation bursts were in the top 25 references, with the strongest occurring between 2008 and 2016. Recently, four articles remained in the period of citation bursts, among which three are worthy of attention. Ott et al. [11]demonstrated the feasibility, safety, and immunogenicity of a vaccine targeting multiple tumour antigens in a single-centre Phase I clinical study (NCT01970358). Six previously untreated patients with high-risk melanoma (stage IIIB/C and IV M1a/b) who underwent

A

Top 25 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	1996 - 2023
Rosenberg SA, 1998, NAT MED, V4, P321, DOI 10.1038/nm0398-321, DOI	1998	71.49	1998	2003	
Nestle FO, 1998, NAT MED, V4, P328, DOI 10.1038/nm0398-328, DOI	1998	80.36	1999	2003	
Thurner B, 1999, J EXP MED, V190, P1669, DOI 10.1084/jem.190.11.1669, DOI	1999	37.72	2001	2004	
Marchand M, 1999, INT J CANCER, V80, P219, DOI 10.1002/(SICI)1097-0215(19990118)80:2219::AID-IJC10>3.0.CO;2-S, DOI	1999	36.58	2001	2004	
Rosenberg SA, 2004, NAT MED, V10, P909, DOI 10.1038/nm1100, DOI	2004	65.99	2005	2009	
Harper DM, 2006, LANCET, V367, P1247, DOI 10.1016/S0140-6736(06)68439-0, DOI	2006	58.63	2006	2011	
Villa LL, 2005, LANCET ONCOL, V6, P271, DOI 10.1016/S1470-2045(05)70101-7, DOI	2005	42.41	2006	2010	
Villa LL, 2007, NEW ENGL J MED, V356, P1915, DOI 10.1056/NEJMoa061741, DOI	2007	45.54	2007	2012	
Paavonen J, 2007, LANCET, V369, P2161, DOI 10.1016/S0140-6736(07)60946-5, DOI	2007	43.52	2008	2012	
Garland SM, 2007, NEW ENGL J MED, V356, P1928, DOI 10.1056/NEJMoa061760, DOI	2007	41.46	2008	2012	
Paovonen J, 2009, LANCET, V374, P301, DOI 10.1016/S0140-6736(09)61248-4, DOI	2009	37.9	2010	2014	
Kantoff PW, 2010, NEW ENGL J MED, V363, P411, DOI 10.1056/NEJMoa1001294, DOI	2010	91.67	2011	2015	
Hodi FS, 2010, NEW ENGL J MED, V363, P711, DOI 10.1056/NEJMoa1003466, DOI	2010	90.34	2011	2015	
Kantoff PW, 2010, J CLIN ONCOL, V28, P1099, DOI 10.1200/JCO.2009.25.0597, DOI	2010	37.1	2011	2015	
Topalian SL, 2012, NEW ENGL J MED, V366, P2443, DOI 10.1056/NEJMoa1200690, DOI	2012	87.03	2013	2017	
Brahmer JR, 2012, NEW ENGL J MED, V366, P2455, DOI 10.1056/NEJMoa1200694, DOI	2012	61.69	2013	2017	
Pardoll DM, 2012, NAT REV CANCER, V12, P252, DOI 10.1038/nrc3239, DOI	2012	40.19	2013	2017	
Wolchok JD, 2013, NEW ENGL J MED, V369, P122, DOI 10.1056/NEJMoa1302369, DOI	2013	38.71	2014	2018	
Schumacher TN, 2015, SCIENCE, V348, P69, DOI 10.1126/science.aaa4971, DOI	2015	41.1	2016	2020	
Larkin J, 2015, NEW ENGL J MED, V373, P23, DOI 10.1056/NEJMoa1504030, 10.1056/NEJMc1509660, DOI	2015	39.21	2016	2020	
Rizvi NA, 2015, SCIENCE, V348, P124, DOI 10.1126/science.aaa1348, DOI	2015	35.92	2016	2020	
Ott PA, 2017, NATURE, V547, P217, DOI 10.1038/nature22991, DOI	2017	89.93	2018	2023	
Sahin U, 2017, NATURE, V547, P222, DOI 10.1038/nature23003, DOI	2017	69.9	2018	2023	
Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21492, DOI	2018	55.36	2019	2023	
Keskin DB, 2019, NATURE, V565, P234, DOI 10.1038/s41586-018-0792-9, DOI	2019	44.79	2019	2023	

B

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1947 - 2023
active specific immunotherapy	1991	49.96	1991	2004	
malignant melanoma	1991	21.74	1991	2003	
cell	1991	21.07	1991	2000	
immunization	1992	22.78	1992	2006	
tumor vaccine	1992	21.36	1992	2003	
gene transfer	1993	26.27	1993	2008	
gene therapy	1994	30.98	1994	2002	
interleukin 2	1995	30.18	1995	2003	
gene	1992	26.08	1995	2005	
t lymphocyte	1995	22.34	1995	2005	
interferon gamma	1995	21.45	1995	2004	
cytotoxic t lymphocyte	1997	43.27	1998	2007	
in vivo	1996	22.46	1998	2008	
colony stimulating factor	1995	28.45	1999	2006	
tumor antigen	1995	21.7	1999	2005	
peptide	1997	27.48	2000	2005	
induction	1993	27.39	2001	2006	
tumor immunity	1991	21.57	2004	2012	
type 16	2006	20.74	2006	2012	
particle vaccine	2006	47.58	2007	2012	
young women	2006	25.11	2007	2014	
suppressor cell	2010	23.56	2014	2021	
open label	2014	33.34	2017	2023	
immune checkpoint inhibitor	2016	21.41	2017	2023	
tumor microenvironment	2013	36.43	2018	2023	

Fig. 7. A. T op 25 references with the strongest citation. B. Top 25 keywords with the strongest citation bursts.

therapeutic resection received the vaccine; four patients achieved 25-month progression-free survival after vaccination, and two patients achieved complete radiological response to pembrolizumab after disease recurrence. Sahin et al. [12] were the first to report the use of a personalised mutant vaccine for melanoma in a multicentre Phase I study (NCT02035956). A significant decrease in longitudinal cumulative recurrence and metastatic events was observed before and after vaccination in the enrolled patients ($P < 0.0001$). Keskin et al. [13] developed a multi-epitope individualised neoantigen vaccine as a vaccination strategy for patients with glioblastoma in a clinical trial (NCT02287428). Single-cell T-cell receptor analysis was used to confirm that neoantigen-specific T cells from the peripheral blood could migrate to the intracranial glioblastoma, thus changing the immune environment of the tumour.

Through the analysis of high-frequency keywords, we can further understand research trends and focus on topics in this field to provide new ideas for researchers. As shown in Fig. 8A, a cluster analysis was performed on keywords related to cancer vaccines. , The keywords in the figure were divided into four clusters according to their colours. Cluster 1 is concerned with the relationship between cancer vaccines and immunotherapy. The keywords used were immunotherapy and vaccines. Cluster 2 concerned the application of dendritic cells to tumour immunity, with the main keywords being dendritic cells, expression, and T cells. Cluster 3 was concerned with the development and mechanisms of cancer vaccines, and the main keywords were antigen, response, and induction. Cluster 4 included vaccination strategies for cancer treatment. The keywords used were cancer, vaccination, and cervical cancer. With the development of tumour precision medicine, cancer vaccines have become important owing to their individualised targeting effects.

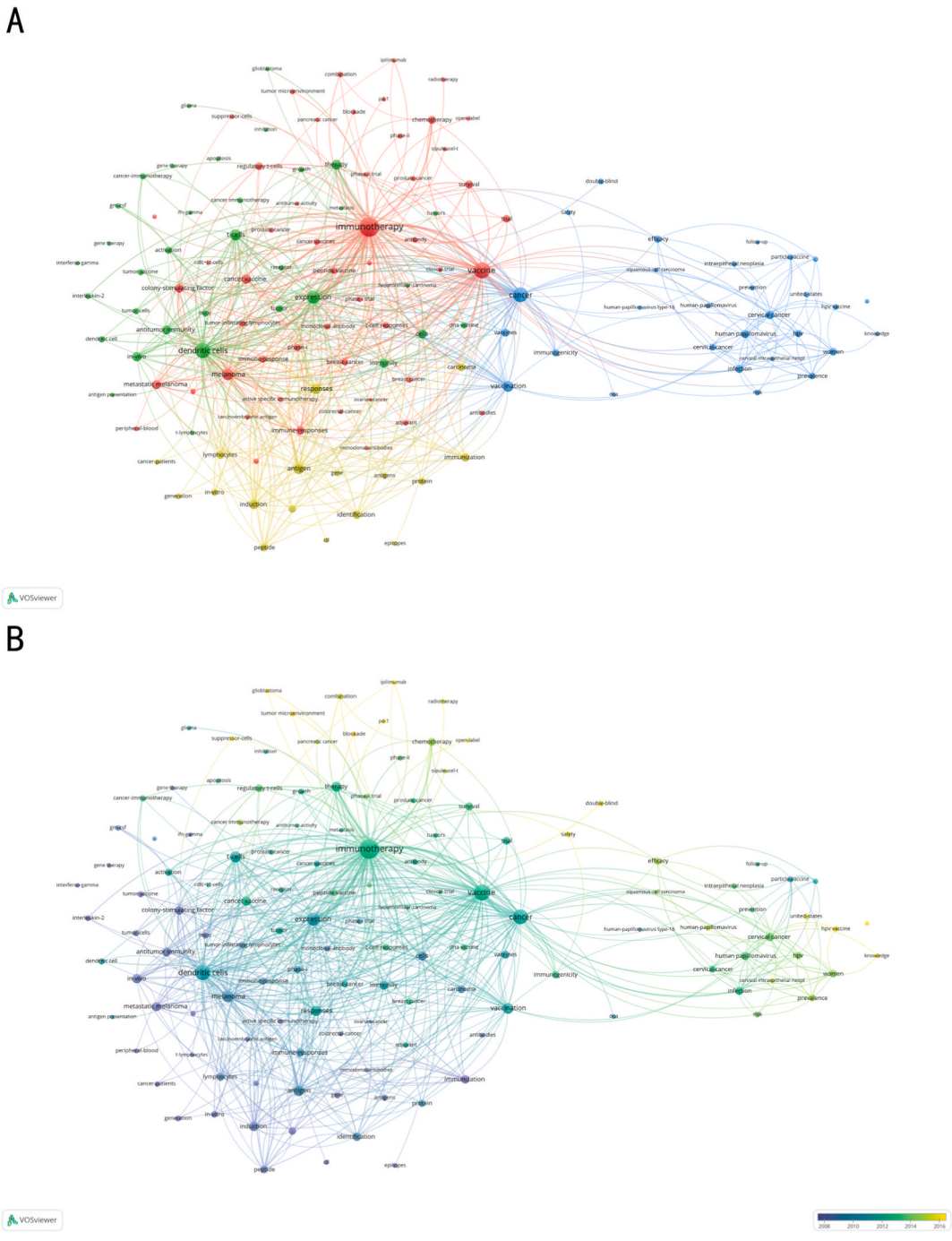

Fig. 8. A. Network visualization map of keywords by VOS viewer. B. Network visualization map of keywords by timeline by VOS viewer.

Starting from basic research on cancer vaccines, corresponding drug development and clinical trials have also begun, and supporting vaccination strategy management has become indispensable.

Based on the cluster analysis of keywords and the results of keyword outbreaks, basic research on cancer vaccines has made progress. From this, we can predict four potential research hotspots and frontiers, namely ‘‘immune checkpoint inhibitors’’, ‘‘tumour microenvironment’’, ‘‘T-cell suppressor’’, and ‘‘dendritic cells".

(1) Immune checkpoint inhibitors:

Since the approval of ipilimumab in 2011, immunotherapy has gradually played an important role in cancer treatment, and more immune checkpoint inhibitors (ICIs), including PD-1/PD-L1 and CTLA-4 inhibitors, have been introduced [14].

However, immune checkpoint inhibitors and cancer vaccines have limitations in immunotherapy [15]. Successful anti-tumour response to cancer vaccines depends on the recognition of specific tumour antigens. The effectiveness of cancer vaccines is significantly reduced when the expression of these antigens is down-regulated or lost [12,16]. Clinical trials [13,17,18] of BCG and neoantigen vaccines against associated cancers have also identified deletion or downregulation of major histocompatibility complex (MHC) molecules as another mechanism of resistance. Additionally, the immune response induced by cancer vaccines is influenced by the TME, which is highly immunosuppressive [19–21]. The limitations of ICIs are mainly due to the high incidence of primary and acquired resistance [22,23]. Moreover, immune-related adverse events (irAEs) induced by ICIs use limiting immunotherapy [24].

The therapeutic limitations of These two immunotherapies limit their ability to achieve improved clinical outcomes. As research has progressed, the combination of the two therapies has shown good synergistic effects. Comparative studies have shown that the combination of cancer vaccines and immune checkpoint inhibitors is more effective than single-drug therapy [25,26]. A Phase II clinical study on locally advanced or metastatic sarcomas demonstrated the synergistic effect of pembrolizumab and TVEC and achieved an overall response rate of 35 % [27]. In a similar clinical study, pembrolizumab and TVEC were used to treat melanoma, with an ORR of 61.9 % (95%CI, 38.4–81.9 %) and complete response of 33.3 % (95%CI, 14.6–57 %) [28].

Cancer vaccines are ideal for use in patients undergoing surgical resection, chemotherapy, or radiation, all of which activate the immune response [2]. ICIs are cell surface receptors that regulate the immune response. They can prevent excessive activation of the immune system and achieve self-tolerance [29]. At this stage, the combination of ICIs with cancer vaccines can induce an anti-tumour immune response more efficiently and overcome the immunosuppressive tumour microenvironment [15].

(2) Tumor microenvironment:

The TME comprises cancer cells, infiltrating immune cells, interstitial cells, and other heterogeneous cell populations [30]. Various cellular interactions in the TME result in inadequate antigen presentation, preventing effective antitumor immune responses [31]. Additionally, cancer cells acquire immune escape through various mechanisms [32]. Understanding these mechanisms necessitates the search for novel immunotherapeutic strategies.

Cancer vaccines mainly achieve their therapeutic goals by enhancing tumour-specific T-cell immunity [33]. Immunosuppressive TME prevents vaccine-induced T cells from entering the tumour, leading to T cell and NK cell depletion, and allows cells with inhibitory phenotypes to accumulate [34]. These tumours, known as “cold” tumours, are not immunogenic in the absence of tumour infiltrating lymphocytes (TILs). In contrast, “hot” tumours are immunogenic and induce an immune response [35,36]. Based on this theory, how to transform a “cold” tumour into a “hot” tumour, and overcome immunosuppressive TME, thus induce a strong tumour-specific immune response has become a difficult problem for cancer vaccines to solve.

Currently, it is feasible to add adjuvants to routine vaccines for immunosuppressive disorders of the TME [34]. In addition, in situ vaccines (ISVs) are considered to be a treatment that can overcome immunosuppression of TME [37]. In situ vaccines are designed to induce and stimulate specific immune responses at tumour sites to produce sustained antitumor effects. This is expected to transform the TME into an immune environment enriched with activated cytotoxic T cells [31]. Notably, the cancer vaccines mentioned above are also highly effective in inducing an anti-tumour immune response and overcoming the immunosuppressive TME when used in combination with ICIs [15].

(3) Dendritic cells:

Most immunotherapy strategies are based on specialised antigen-presenting cells (APCs) to present tumour antigens [38], and dendritic cells (DCs), macrophages, and B cells are generally considered the three major populations of APCs [39,40]. Dendritic cells have the unique ability to transport tumour antigens to draining lymph nodes to initiate antitumor T cells [41–44]. Therefore, dendritic cells have been the focus of cancer immunotherapy because of their role in inducing a protective adaptive immune response [45,46].

Considering the role of DCs in the immune response, enhancing the function of DCs or increasing the number of DCs has become the focus of research. Dendritic cell vaccines are a strategy for exogenous amplification of dendritic cells. Currently, there is one whole-cell DC vaccine approved by the FDA, sipuleucel-T [47]. However, the clinical efficacy these of vaccines is mostly limited. The immunosuppressive TME is an important factor that blocks the infiltration, proliferation, and effects of T cells [45].

Although considerable resources have been invested in the development of DC vaccines, their clinical benefits remain satisfactory [48]. Extensive clinical trials and evaluations are underway [49,50]. In particular, the combination of DC vaccines with other therapies shows good clinical prospects. A Phase III trial(NCT00045968) evaluated the efficacy of a whole-cell DC vaccine in combination with tumour (glioblastoma) resection, temozolomide, and radiotherapy, and the results indicated the safety and potential efficacy of the therapy [51]. A prospective study (NCT02956551) confirmed the safety and tolerability of a neoantigen-based DC vaccine for the treatment of advanced metastatic lung cancer, providing new evidence for neoantigen vaccine treatment of lung cancer [52].

It is worth mentioning that the development of the DC vaccine has been ongoing. Currently, there are two generations of the DC vaccine [53]. The first generation of DC vaccines consist of natural DC isolated in vivo or immature monocyte-derived DCs (mo-DCs) generated in vitro [54,55]. Although the clinical efficacy of this DC vaccine is limited, its safety and clinical feasibility have been preliminarily confirmed [56,57]. Second-generation DC vaccines, which use fully mature mo-DCs, mostly use antigenic peptides from tumour antigens [58,59]. They performed better than first-generation DC vaccines in most clinical studies [48]. The research and

development focus of third-generation DC vaccines has shifted to the nature and origin of DCs, and the special role of DC subgroup type 1 (cDC1) in tumour immunity has been discovered [60,61]. DC vaccines based on this specific subgroup may provide insight into next-generation cancer therapies.

(4) T-cell suppressor:

T-cell suppressors refer to several factors that can inhibit T-cell activity and impair T-cell responses in patients with cancer [62]. These include the immunosuppressive TME, activated myeloid-derived suppressor cells (MDSC) and regulatory T cells (Tregs). These factors can reduce the therapeutic efficacy of cancer vaccines.

MDSC are myeloid immune cells; when they migrate to the tumour and activate it, they promote immunosuppression by interacting with the TME [63]. MDSC can impair T cell and natural killer cell responses, especially by inhibiting the activation and efferent function of CD8+T cells [64–66], which inhibit T cell proliferation mainly through the consumption of amino acids, including cysteine, L-arginine, and tryptophan [67,68]. Current solutions include blocking the recruitment and migration of MDSC to the tumour [69,70], increasing the consumption of MDSC (such as some chemotherapy drugs) [71,72], and inducing the differentiation of immature bone marrow cells [73,74].

Tregs are a subset of cells that regulate the autoimmune response and were previously known as suppressor T cells [75]. They protect the body from autoimmune effects; however, paradoxically, they can also be used by tumour cells to disrupt the body's anti-tumour immune response [76]. They are produced by the thymus and have the ability to migrate to local tumours, where they actively regulate T cell activation and proliferation, resulting in their inhibition [77]. New targets or depletion of Tregs is a popular research direction for enhancing the efficacy of cancer immunotherapy. Current strategies include cyclophosphamide [75], anti-RANKL antibody denosumab [78], interference with the main transcription factor FoxP3 [79], and specific COX-2 inhibitors [80].

The above describes some of the factors that affect the efficacy of cancer vaccines, which are key issues that need to be addressed in the future.

Four potential research hotspots are described and analysed above, and we propose that future research should focus on the synergistic effects of immune checkpoint inhibitors, cancer vaccines, and DC vaccines. Additionally, addressing the immunosuppressive effects resulting from the interaction between T-cell suppressor factors and the TME is a crucial challenge in enhancing the efficacy of cancer vaccines, which also represents a prominent area for further research.

5. Strengths and limitations

This study is the first to use bibliometric analysis and visualization tools to analyse the global trend of cancer vaccine research, systematically displaying the development, current situation, and frontiers of related research. The limitations of this study are as follows: First, we only retrieved and collected literature data from the WOSCC database, which may have missed important studies in PubMed, Embase, and other databases. Second, this study only included literature data on oncology from the WOSCC database, which may have overlooked some important cross-disciplinary studies. Third, only English literature was included in this study, and important studies in other languages may have been missed. Finally, only the journal's impact factors and category quartiles were evaluated, and the quality of the articles included in the study was not assessed.

6. Conclusion

In summary, cancer vaccine-related research is moving from preclinical research and clinical trials to clinical applications, and the number of related publications will continue to surge over the next few years. The United States has the largest proportion of research in this field and the highest quality and influence of articles and plays an important role in this field. Currently, cancer vaccine research is focused on how to improve clinical benefits, "immune checkpoint inhibitors", "tumour microenvironment", "dendritic cells," and "T-cell suppressor" may be the future research focus.

Data availability statement

The original data presented in the article are included in the article/Supplementary Material/referenced, further inquiries can be directed to the corresponding author.

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CRediT authorship contribution statement

Rui Yu: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Fangmin Zhao:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Zeting Xu:** Writing – review & editing. **Gaochenxi Zhang:** Writing – review & editing. **Bingqing Du:** Writing – review & editing. **Qijin Shu:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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