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Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: www.tandfonline.com/journals/khvi20

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To cite this article: Zhaoming Song , Chen Yang , Jingyu Gu , Ruisi Qu , Yun Xie , Yanao Guo , Xun Nong, Zhouqing Chen & Zhong Wang (2025) The hotspots and publication trends in glioblastoma and CAR-T immunotherapy: A bibliometric analysis, Human Vaccines & Immunotherapeutics, 21:1, 2509483, DOI: 10.1080/21645515.2025.2509483

To link to this article: https://doi.org/10.1080/21645515.2025.2509483

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2509483
https://doi.org/10.1080/21645515.2025.2509483

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RESEARCH ARTICLE

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The hotspots and publication trends in glioblastoma and CAR-T immunotherapy: A bibliometric analysis

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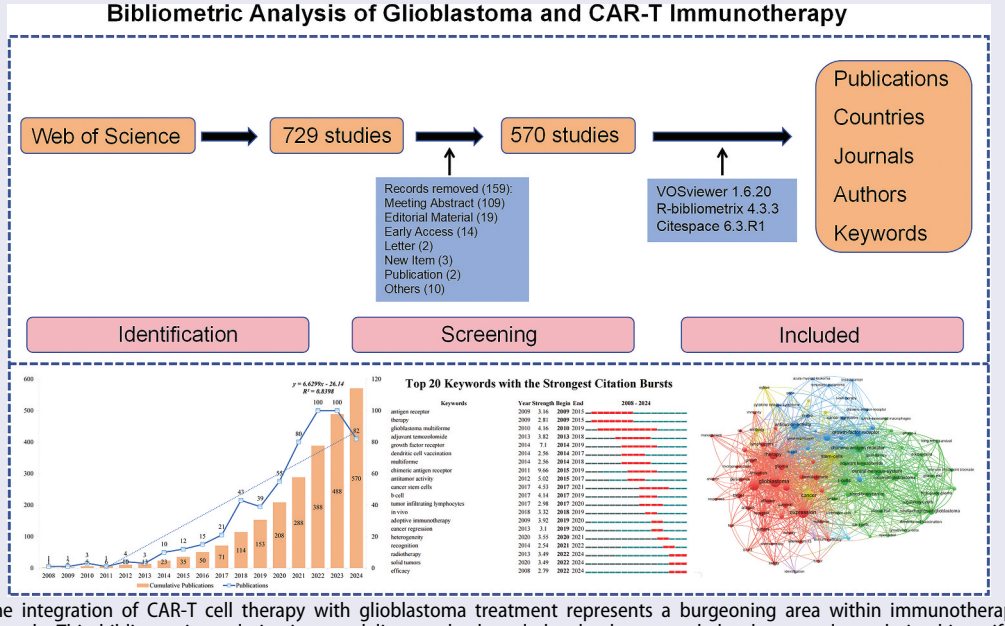
ABSTRACT

In recent years, chimeric antigen receptor T cell (CAR-T) immunotherapy has made considerable progress in the treatment of glioblastoma. The aim of this study was to comprehensively explore the prospects and future trends of CAR-T immunotherapy for glioblastoma through systematic bibliometric analysis. Publications pertaining to glioblastoma and CAR-T immunotherapy from 2008 to 2024 were extracted from the Web of Science Core Collection. Utilizing VOSviewer (version 1.6.20), CiteSpace (version 6.3.R1), and R 4.3.3, this study concentrated on evaluating contributions from countries, institutions, authors, and journals, while also identifying research hotspots and emerging trends. A total of 570 publications were identified, demonstrating an annual growth rate of 31.71%. The USA led the field with 269 publications, followed by China (113). The University of Pennsylvania, Harvard University, and the University of California System emerged as the most prolific institutions. *Frontiers in Immunology* published the most articles (42), while *Clinical Cancer Research* garnered the highest number of citations (2,867). Recent keyword bursts (2022–-2024) underscored an increasing focus on combination therapy approaches and outcomes, particularly emphasizing "radiotherapy" (strength 3.49), "solid tumor" (strength 3.49), and "efficacy" (strength 2.79). In recent years, research on CAR-T immunotherapy for glioblastoma has gradually shifted from the exploration of basic mechanisms to the application of clinical combination therapy, and this shift in research direction indicates that CAR-T immunotherapy has a relatively mature technology and great clinical translation potential. In the coming years, CAR-T immunotherapy is expected to usher in a golden era and benefit more patients suffering from glioblastoma.



The integration of CAR-T cell therapy with glioblastoma treatment represents a burgeoning area within immunotherapy research. This bibliometric analysis aims to delineate the knowledge landscape and developmental trends in this swiftly advancing field. While earlier investigations concentrated on fundamental mechanisms, current trends indicate a heightened focus on combination therapeutic strategies and treatment outcomes.

ARTICLE HISTORY

Received 25 February 2025
Revised 2 May 2025
Accepted 17 May 2025

KEYWORDS

Glioblastoma; CAR-T immunotherapy; bibliometric analysis; tumor microenvironment; immunotherapy efficacy

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21645515.2025.2509483

Introduction

Glioblastoma (GBM) is recognized as the most aggressive primary brain tumor, with a median survival rate of only 12 to 15 months despite standard treatment modalities, which encompass surgery, radiation, and chemotherapy.[1] The dismal prognosis associated with this malignancy is primarily ascribed to the tumor's heterogeneity, invasive characteristics, and the presence of the blood-brain barrier, which significantly impedes effective therapeutic delivery.[2] In recent years, chimeric antigen receptor T-cell (CAR-T) immunotherapy has emerged as a promising treatment modality for various cancers, including glioblastoma, signifying a substantial advancement in the field of cancer immunotherapy.[3,4]

The CAR-T cell therapy entails the genetic engineering of a patient's T cells to express chimeric antigen receptors that specifically target tumor antigens.[5] The notable success of CAR-T cells in the treatment of hematological malignancies has prompted heightened interest in adapting this approach for solid tumors, particularly glioblastoma.[6] However, the implementation of CAR-T cells in the treatment of glioblastoma encounters distinct challenges, such as antigen heterogeneity, an immunosuppressive tumor microenvironment (TEM), and concerns regarding potential central nervous system toxicity.[7,8]

Research in this domain has proliferated rapidly over the past decade, with numerous studies investigating various facets including target antigen selection, optimization of CAR design, delivery strategies, and combination therapies.[9] The inaugural clinical trial utilizing CAR-T cells for glioblastoma was documented in 2016, underscoring both the feasibility and potential hurdles associated with this therapeutic approach.[10] Since that time, there has been a notable increase in both preclinical and clinical research, culminating in significant advancements in the understanding of the complexities inherent in CAR-T cell therapy for glioblastoma.[11]

Given the swift evolution and increasing significance of this field, a comprehensive analysis of research trends, prominent contributors, and emerging directions is imperative for grasping the current landscape and identifying future opportunities. Bibliometric analysis offers a systematic methodology for evaluating the scientific literature and discerning patterns in research development, collaboration networks, and emerging trends.[12]

Several bibliometric studies have been conducted in related fields. Du et al. (2022) examined research trends in glioblastoma treatment strategies,[13] while Zhang et al. (2022) investigated the evolution of CAR-T cell therapy across various cancer types.[14] Nonetheless, a comprehensive bibliometric analysis specifically targeting CAR-T immunotherapy in glioblastoma has yet to be reported.

Therefore, based on the Web of Science Core Collection (WoSCC), this study employed bibliometric tools to elucidate publication trends, influential contributors, leading collaborators, and emergent frontier topics within the realm of CAR-T immunotherapy for glioblastoma.

Materials and methods

Search strategy

A literature search was conducted utilizing the WoSCC database (https://www.webofscience.com/wos/woscc/basic-search) on November 11, 2024. The search formula was (TS=(CAR-T OR CAR T cells OR Chimeric Antigen Receptor T-Cell Immunotherapy OR CAR T Cell-Based Immunotherapy)) AND TS=(Glioblastoma* OR Glioblastoma Multiforme* OR Giant Cell Glioblastoma*). Only articles published in English were included in the analysis. The collected data encompassed information on countries, institutions, journals, authors, year of publication, and keywords, which were subsequently analyzed.

Data analysis

VOSviewer (version 1.6.20) is a bibliometric analysis software that can extract key information from numerous publications.[15] The software primarily performs the following analyses: the collaboration networks of authors, countries, and institutions; journal co-occurrence and coupling networks; and keyword co-occurrence analysis. In the visualization generated by VOSviewer, a node represents an entity, such as a country, institution, journal, or author. The size and color of the nodes correspond to the quantity and classification of these entities, respectively. Additionally, the thickness of the lines connecting the nodes indicates the extent of collaboration or co-citation among the entities.

CiteSpace (version 6.3.R1) is another software developed by Professor Chen C for bibliometric analysis and visualization.[16] In our study, CiteSpace was applied to analyze references with Citation Bursts. The time slicing was set from 2008 to 2024 with a one-year interval. The top 5 most cited items per slice were selected for analysis. Pruning was performed using pathfinder and pruned merged network approaches.

The R package "bibliometrix" (version 4.3.3) (https://www.bibliometrix.org) was used to map the global distribution of research output and evaluating the impact of authors, journals, and institutions of glioblastoma and CAR-T immunotherapy research.[17] The quartile and impact factor of journals were sourced from the Journal Citation Reports (JCR) 2023. The JCR quartiles classify journals into four distinct tiers, with Q1 denoting the highest level of academic quality. The h-index is a measure that shows that a researcher has at least h publications and that each of these publications has been cited at least h times.[18,19]

Results

Overall characteristics

The literature screening process identified 729 studies from the Web of Science Core Collection, with 159 records excluded (including 109 meeting abstracts, 19 editorial materials, 14

early access articles, and other document types), resulting in 570 articles for final analysis (Figure 1). Basic bibliometric indicators showed that these publications were produced by 3,715 authors from 223 sources, with an international co-authorship rate of 21.58% and an average of 8.89 coauthors per document. The articles received an average of 48.67 citations per document and contained 26,640 references in total (Figure 2a). The publication trend analysis revealed a steady increase in research output from 2008 (1 publication) to 2024 (82 publications), with a significant annual growth rate of 31.71%. The trend line followed a linear equation ($y = 6.6299\times - 26.14$, $R^2 = 0.8398$), with particularly rapid growth observed between 2019 and 2022, reaching peak annual publications of 100 in 2022–2023 (Figure 2b).

Analysis of countries

The analysis of geographical distribution revealed significant disparities in research contributions across different countries. Among the top 20 countries in research output, the USA dominated the research landscape with 269 publications (47.2% of total output), followed by China with 113 publications (19.8%) and Germany with 31 publications (5.4%) (Figure 3a, Table S1). When examining collaboration patterns, Single Country Publications (SCP) and Multiple Country Publications (MCP) ratios showed varying degrees of international engagement. The USA had 224 SCP and 45 MCP (MCP ratio = 0.167), while China demonstrated similar collaboration patterns with 92 SCP and 21 MCP (MCP ratio = 0.186) (Table S1). The international collaboration network analysis revealed that among the 23 countries involved in international collaborations with a minimum of 3 articles, the USA had the highest number of collaborative links (106), followed by China (39) and Germany (27), indicating their roles as major hubs in the global research network (Figure 3b).

Analysis of institutions

The institutional analysis revealed a strong concentration of research activity among leading academic and medical centers. The University of Pennsylvania emerged as the most productive institution with 176 publications, followed by Harvard University (117 publications) and the University of California System (103 publications). City of Hope and Baylor College of Medicine rounded out the top five with 99 and 87 publications, respectively (Figure 4a). Among the top institutions, there was a notable presence of specialized cancer research centers, including the Beckman Research Institute of City of Hope (51 publications) and the Helmholtz Association (54 publications). The institutional collaboration network analysis identified robust research partnerships, with University of Pennsylvania having the highest number of collaborative connections (86), while Harvard Medical School (74) and University of California – Los Angeles (53) also demonstrated strong collaborative networks (Figure 4b).

Analysis of journals

The journal analysis revealed diverse publication patterns across multiple scientific outlets, with varying impact factors and citation metrics. Among the top 20 most influential journals, *Frontiers in Immunology* led the publication count with 42 articles (h-index = 18, impact factor = 5.7), followed by *Cancers* with 33 articles (h-index = 13, impact factor = 4.5). The *International Journal of Molecular Sciences and Frontiers in Oncology* also made significant contributions with 19 and 22 publications respectively (Table S2). Notable high-impact journals in the field included *Clinical Cancer Research* (17 articles, impact factor = 10.0) and *Neuro-Oncology* (15 articles, impact factor = 16.4). The citation analysis showed that *Clinical Cancer Research* received the highest number of citations (2,867), followed by *Neuro-Oncology* (2,586). Journal co-citation network analysis identified three key journals with the highest total link strength: *Frontiers in Immunology* (484), *Clinical Cancer Research* (429), and *Cancers* (397) (Figure 5a). The journal coupling analysis further demonstrated strong interconnections, with *Frontiers in Immunology* showing the highest coupling strength (1,282), followed by *Cancers* (469) and *Frontiers in Oncology* (405) (Figure 5b). Most journals fell into the first quartile (Q1) of their respective categories, with *Nature Medicine* having the highest impact factor (58.7) among the journals, though with a relatively smaller number of publications (5 articles).

Analysis of authors

The author analysis identified 3,715 researchers contributing to the field, with only 6 authors published single-authored documents, indicating a strong collaborative research environment. Among the top 20 most productive authors, Brown Christine E. emerged as the most influential researcher with the highest h-index (17), g-index (26), and m-index (1.55), publishing 26 articles that garnered 3,517 citations. Second in impact was Forman Stephen J. (h-index = 14, g-index = 18, 18 publications), followed by Sampson John H. (h-index = 14, g-index = 15, 15 publications) (Table S3). The analysis of author collaboration networks revealed distinct research clusters, with Brown Christine E. showing the highest number of collaborative connections (133), followed by Forman Stephen J. (117) and Starr Renate (108) (Figure 6).

Most cited articles

Analysis of citation patterns revealed several highly influential publications in the field. The most cited article was authored by Brown CE et al. (2016) in the *New England Journal of Medicine*, titled "*Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy*," accumulating 1,254 citations (139.33 citations per year).[10] The second most cited article was by O'Rourke DM et al. (2017) in *Science Translational Medicine*, garnering 1,209 citations (151.13 citations per year).[20] Fesnak AD et al.'s (2016)

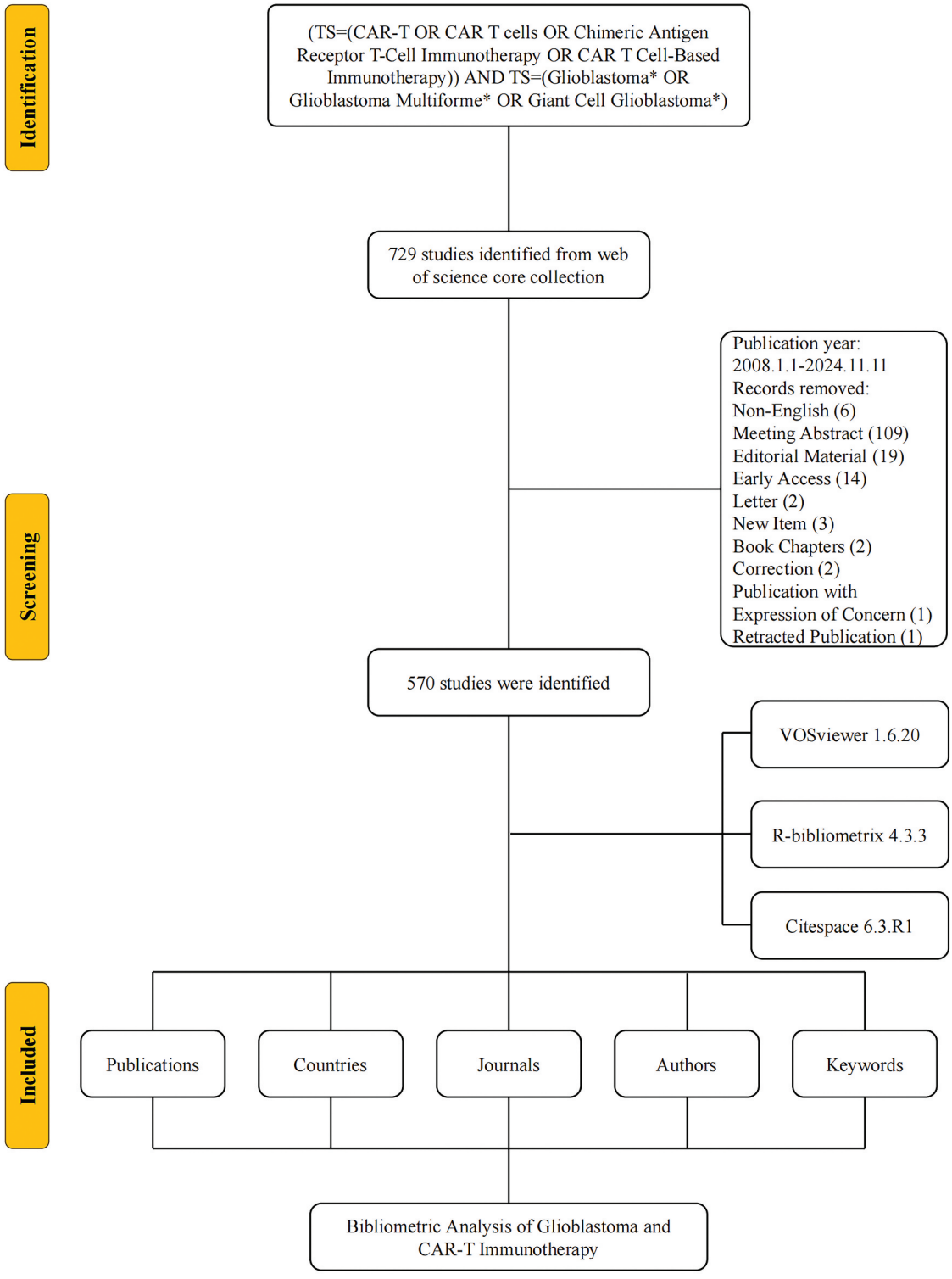

Figure 1. Flowchart of the literature screening process.

review in *Nature Reviews Cancer* ranked third with 776 citations (86.22 citations per year).[21] Recent high-impact publications included Majzner RG et al.'s 2022 article in *Nature* (417 citations, 139.0 citations per year)[22] and Yang KY et al.'s 2022 publication in *Molecular Cancer* (370 citations, 123.33 citations per year),[23] demonstrating rapid citation accumulation. The normalized citation analysis showed that recent publications from 2020–2022 achieved notably high impact, with Jacob F et al. (2020, Cell) and Majzner RG et al. (2022, Nature) having normalized citation rates of 10.76 and 14.45 respectively, indicating growing interest in recent developments in the field.

Analysis of keywords

The keyword analysis revealed the conceptual structure and research trends in the field through both co-occurrence

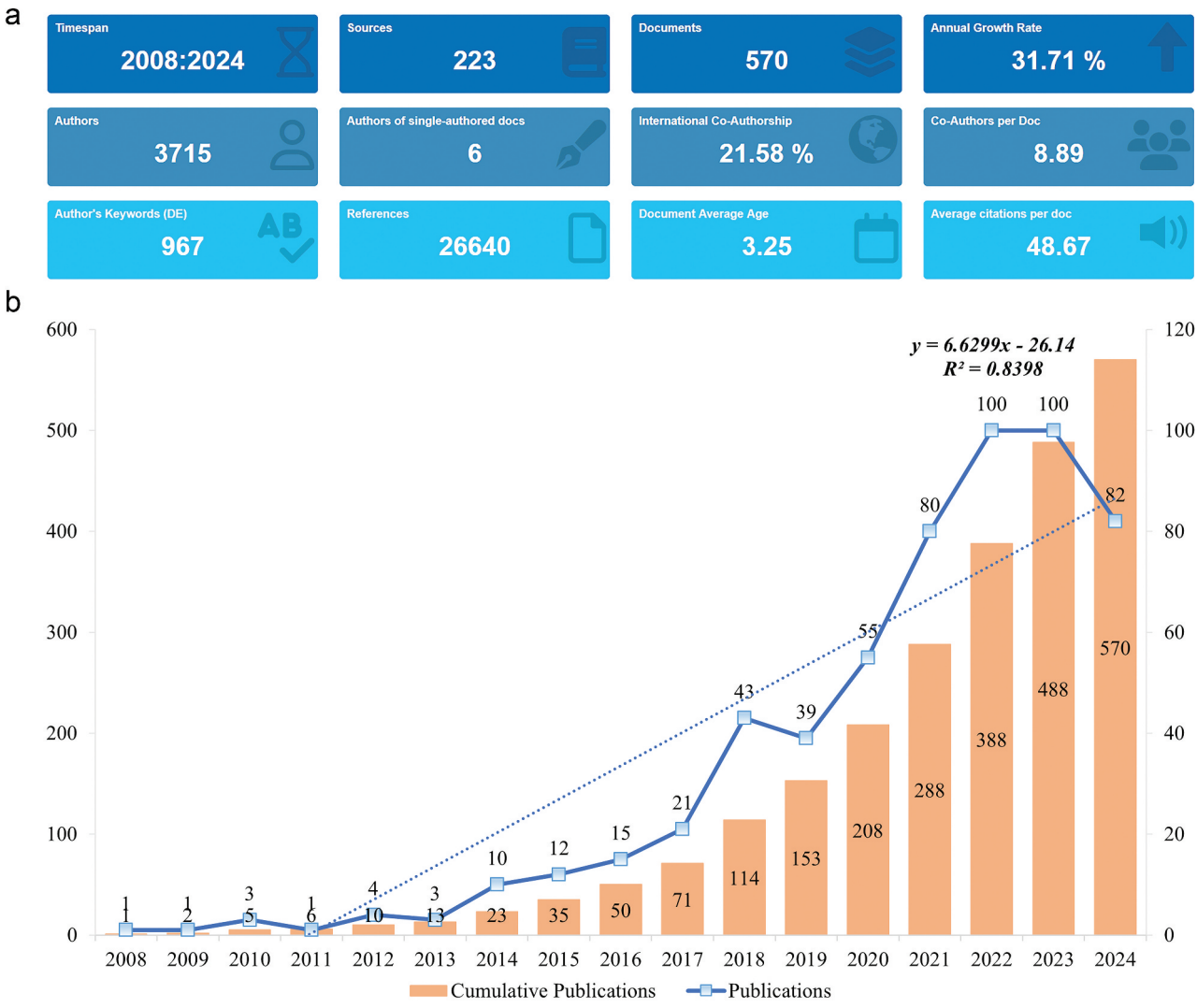

Figure 2. Analysis of general information. (a) Summary information of the included studies. (b) Annual number of publications.

networks and citation bursts. Among the 967 author keywords identified, "glioblastoma" showed the highest frequency (149 occurrences) and strongest total link strength (614), followed by "expression" (120 occurrences, link strength 562) and "immunotherapy" (114 occurrences, link strength 522) (Figure 7). The co-occurrence network analysis identified three major clusters of research themes: 1) basic therapeutic mechanisms and response monitoring (38 items including activation, antigen, efficacy); 2) clinical translation and delivery strategies (34 items including adjuvant temozolomide, blood-brain-barrier); 3) broader immunotherapy applications (18 items including acute myeloid leukemia, breast cancer, and B-cell). Citation burst analysis (Figure 8) revealed significant research trends over time, with "chimeric antigen receptor" showing the strongest citation burst (strength = 9.66, 2015–2019). Recent research hotspots emerging since 2022 focused on "radiotherapy" (strength = 3.49), "solid tumors" (strength = 3.49), and "efficacy" (strength = 2.79), indicating a shift toward practical therapeutic applications and treatment outcomes. The temporal evolution of keywords demonstrated the field's progression from basic receptor studies to more complex therapeutic approaches.

Discussion

General information

This bibliometric analysis of glioblastoma and CAR-T immunotherapy research from 2008 to 2024 revealed significant growth in publication output, with 570 publications from 3,715 authors across 223 journals. The field showed remarkable expansion, particularly after 2020, with an annual growth rate of 31.71% and increasing international collaboration networks. The landscape of current research reveals a clear shift in focus, particularly evident from 2022 onwards, with three dominant emerging trends: the integration of radiotherapy with CAR-T cell therapy, addressing the broader challenges of solid tumors, and a renewed emphasis on treatment efficacy. This evolution in research priorities suggests the field is moving toward combination therapeutic approaches, particularly exploring

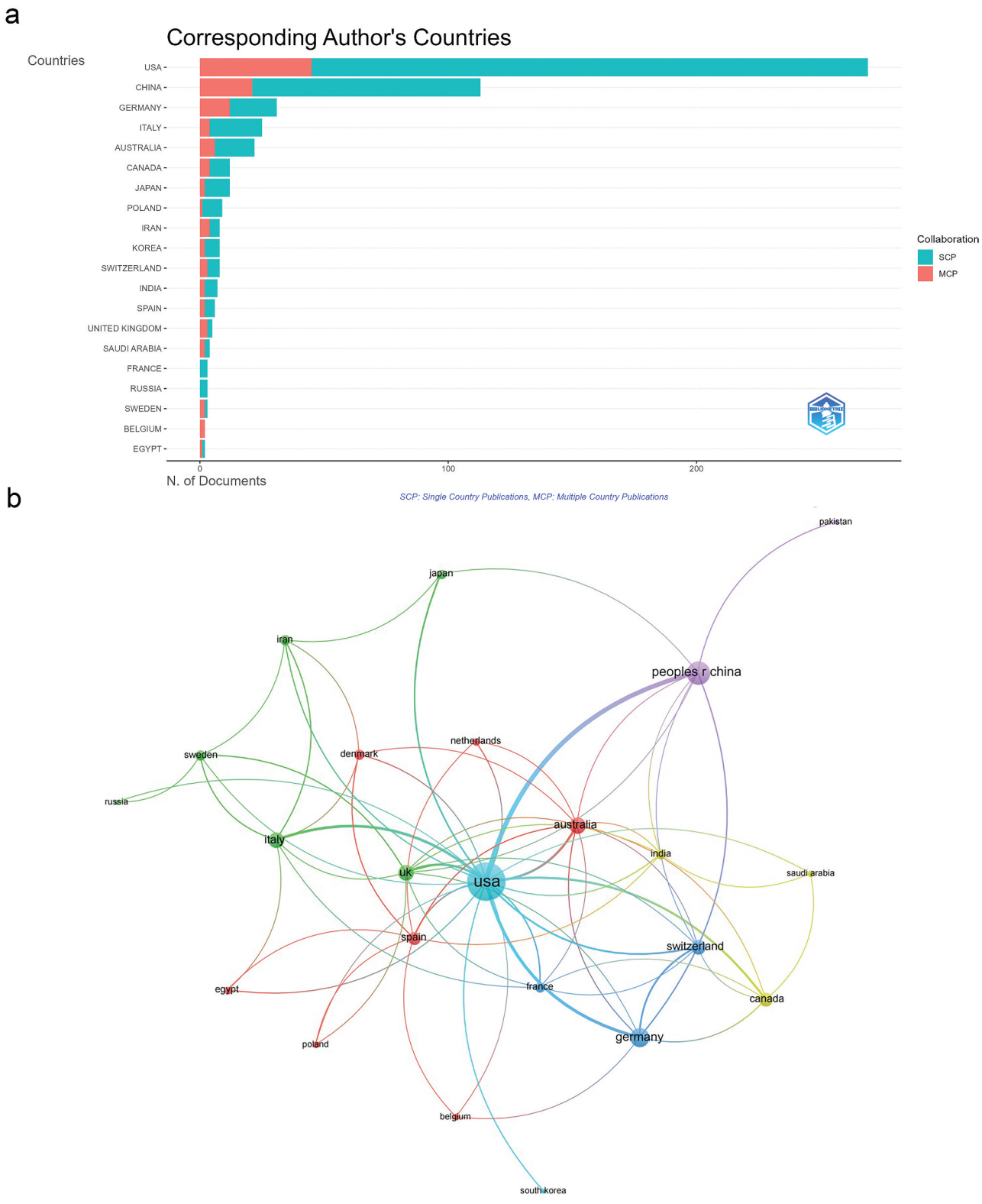

Figure 3. Analysis of countries. (a) Distribution of corresponding author's publications by country. (b) Visualization map depicting the collaboration among different countries.

the synergy between CAR-T cells and radiotherapy, while maintaining a strong focus on improving overall treatment effectiveness.

The journal analysis revealed a strategic focus on high-impact immunology and oncology publications. While *Frontiers in Immunology* led in volume, the substantial presence in *Clinical Cancer Research* and *Neuro-Oncology*, along with highly-cited papers in *Nature Medicine* and *Science Translational Medicine*, demonstrates the field's emphasis on translational research and clinical impact.

Research output showed geographic concentration, with North American and Chinese institutions dominating the

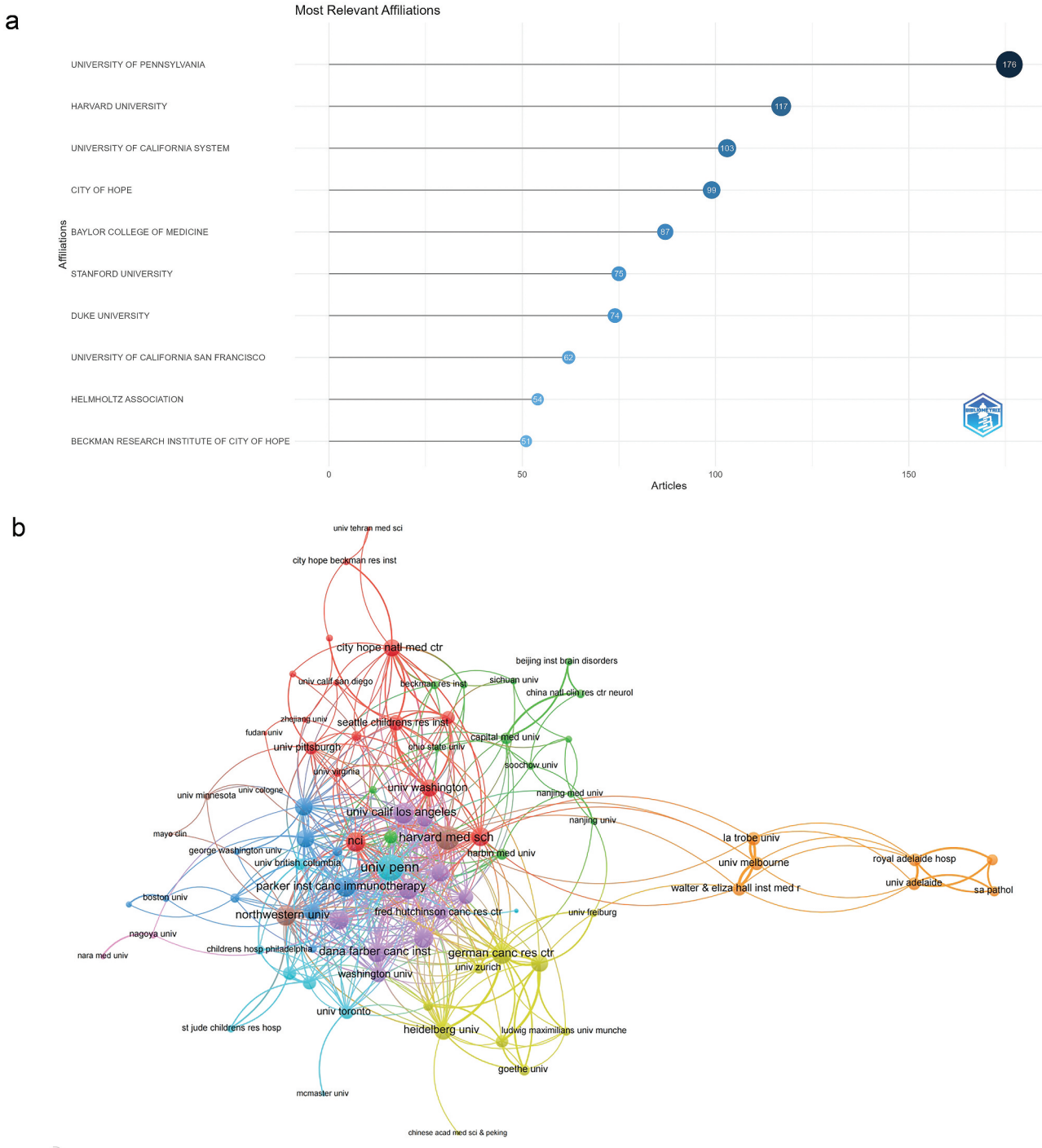

Figure 4. Analysis of institutions. (a) Top ten institutions by article count and rank. (b) Visualization map depicting the collaboration among different institutions.

landscape. The USA's leading position (47.2% of publications) reflects its established research infrastructure, including robust funding mechanisms and advanced manufacturing capabilities. China's strong second position highlights its growing investment in immunotherapy research.

The author analysis identified key research clusters centered around pioneering investigators. Brown Christine E.'s citation metrics reflect breakthrough contributions in CAR-T development, complemented by Forman Stephen J. and Sampson John H.'s work on glioblastoma immunotherapy. The high co-authorship rate (8.89 authors per paper) underscores the multidisciplinary collaboration required in this complex field.

The research landscape was significantly shaped by several landmark publications, most notably Brown et al.'s 2016 study in the New England Journal of Medicine (1,254 citations). This pivotal paper, documenting the first successful CAR-T cell therapy for glioblastoma, marked a critical transition from preclinical research to clinical application. The trial demonstrated tumor regression in a patient with recurrent glioblastoma following IL13Rα2-targeted CAR-T cell therapy, establishing both feasibility and potential efficacy. This

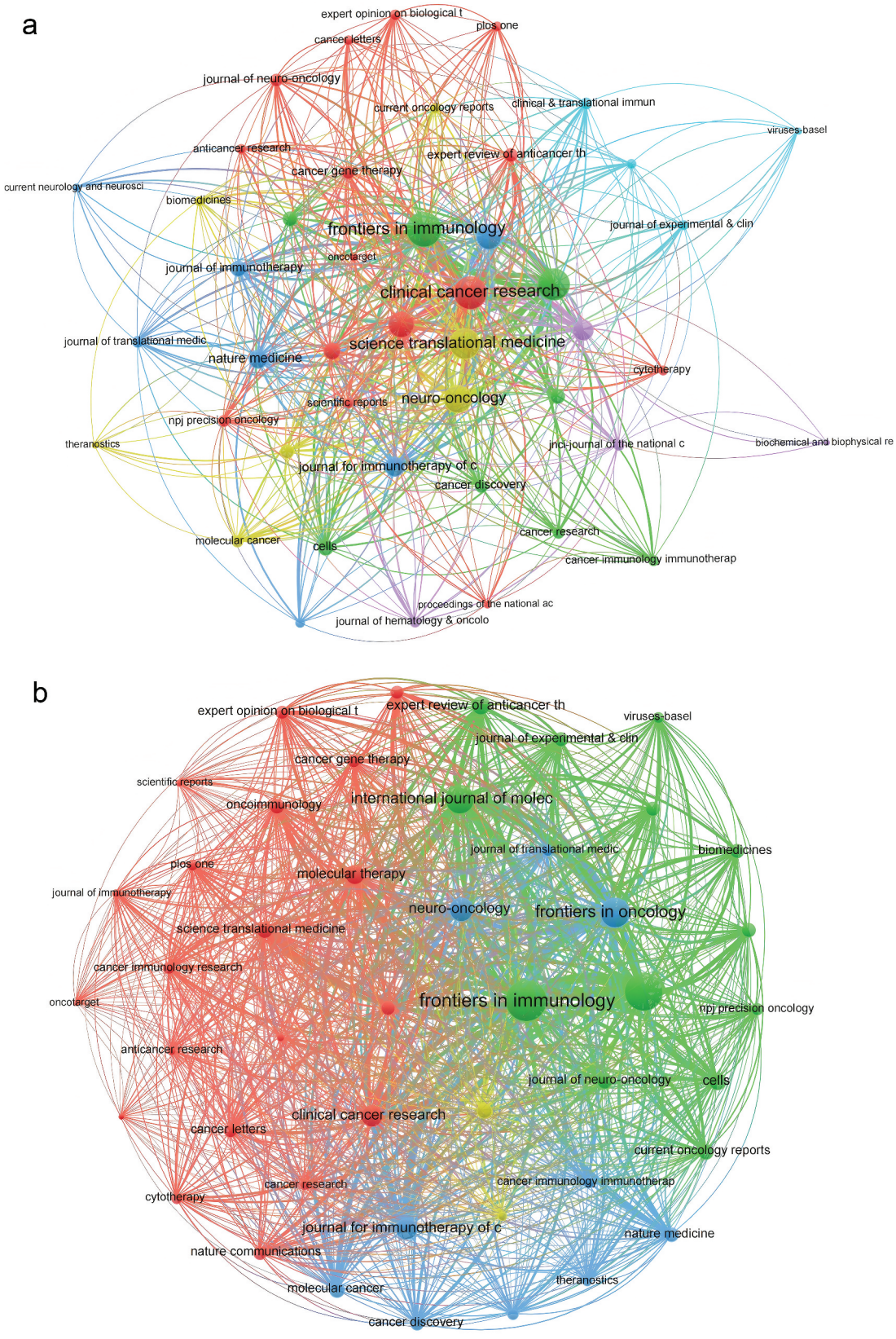

Figure 5. Analysis of journals. (a) Co-occurrence network of journals. (b) Coupling network of journals.

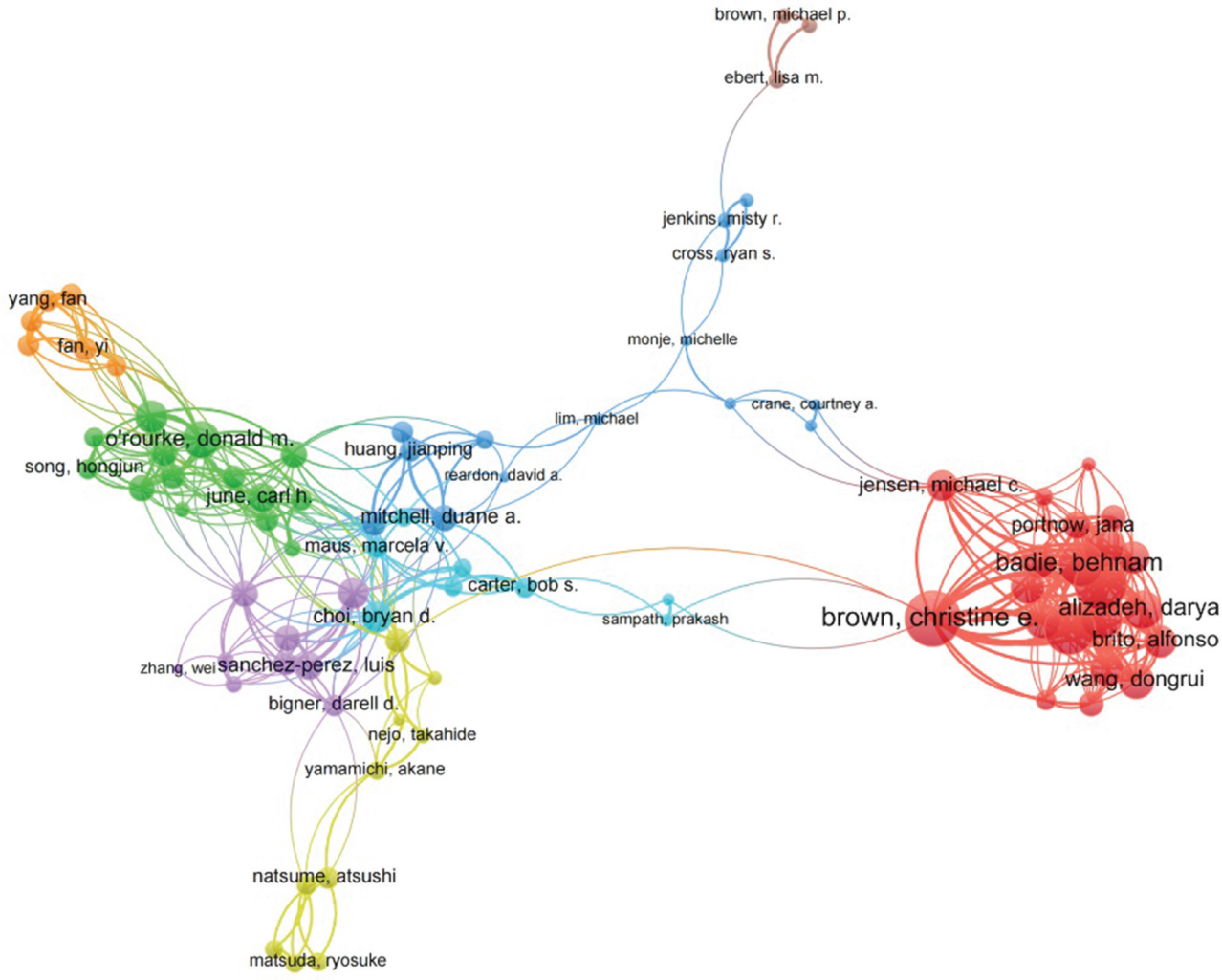

Figure 6. Visualization map depicting the collaboration among different authors.

breakthrough study not only validated the therapeutic concept but also identified key challenges that would shape future research directions, including antigen targeting strategies and the need for improved cell persistence in the tumor microenvironment.[10]

Research hotspots and frontier trends

Based on the keyword co-occurrence network analysis, the research in glioblastoma and CAR-T immunotherapy revealed three distinct clusters representing major research directions.

Basic therapeutic mechanisms and response monitoring

Cluster 1 encompassed 38 items focused on basic therapeutic mechanisms and response monitoring. This largest cluster reflected fundamental aspects of treatment implementation and outcome assessment. The high frequency of terms like "efficacy," "expression," and "immunotherapy" indicates intensive research into optimizing treatment outcomes. Brown et al. (2016) first demonstrated significant tumor regression using IL13Rα2-targeted CAR-T cells, establishing a foundation for monitoring treatment response.[10] This work was further expanded by their 2022 study developing steroid-resistant CAR-T cells, addressing a crucial challenge in managing treatment-related inflammation.[24] The prominence of "microenvironment" and "heterogeneity" indicates growing attention to resistance mechanisms. Jackson et al. (2019) comprehensively mapped these challenges, highlighting how tumor heterogeneity and the immunosuppressive microenvironment limit CAR-T efficacy.[25] Martinez and Moon (2019) further detailed how the brain tumor microenvironment specifically impairs CAR-T cell function, proposing strategies for enhancing cell persistence and activity.[26] Recent work by Luksik et al. (2023) has focused on overcoming antigen heterogeneity, suggesting multi-target approaches as a promising direction.[27] The inclusion of "radiotherapy" and "temozolomide" in this cluster reflects increasing interest in combination approaches. Radiotherapy-induced DNA damage and cell death release tumor-associated antigens (TAA), which activate the immune system and promote the maturation and migration of antigen-presenting cells (APCs), thereby enhancing the anti-tumor activity of CAR-T cells. Moreover, radiotherapy can modify the tumor microenvironment to make it more immunogenic, facilitating the infiltration and expansion of CAR-T cells.[28] In glioblastoma, radiotherapy increased the

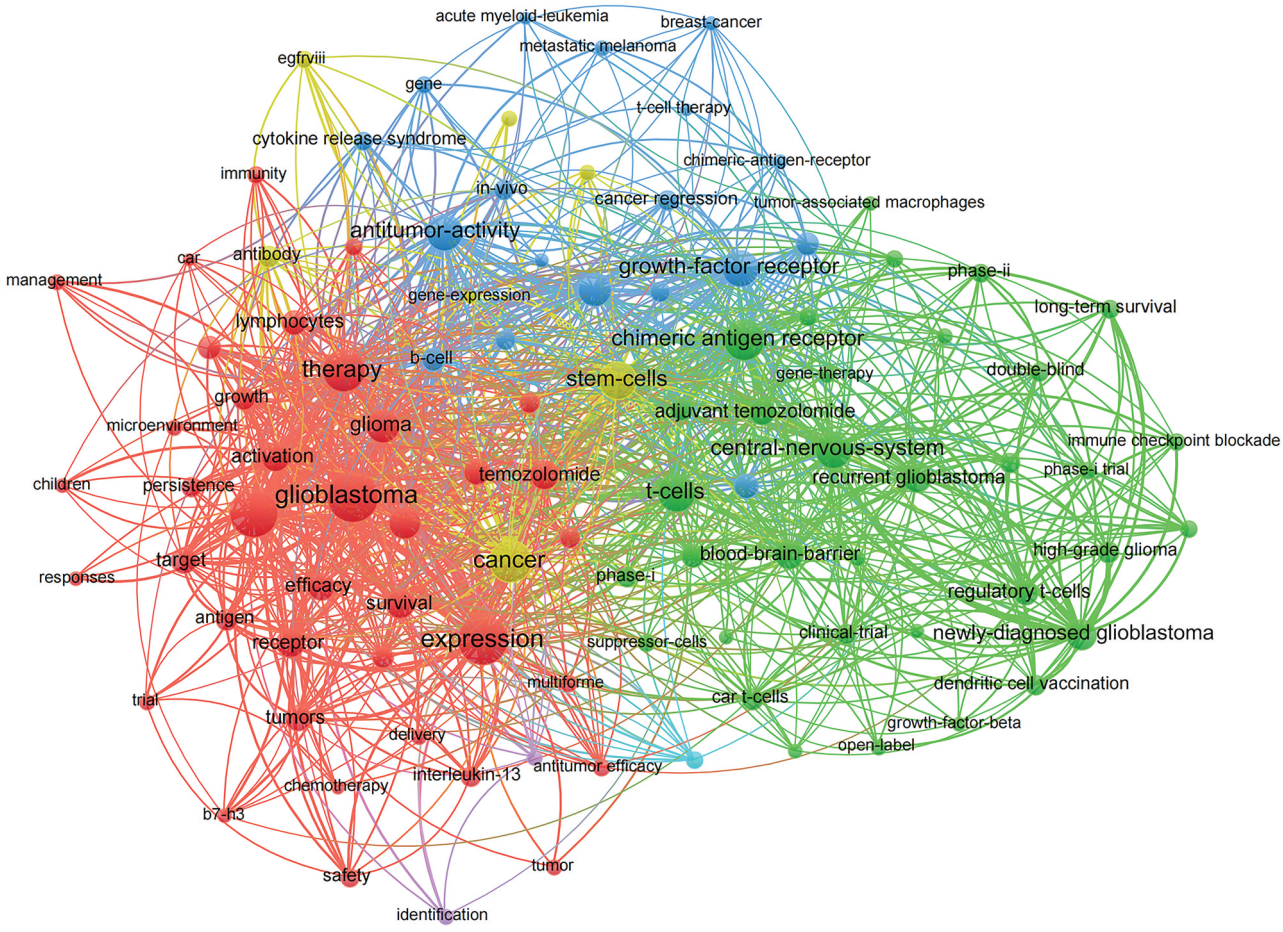

Figure 7. Visual analysis of keyword co-occurrence network analysis.

Keywords	Year	Strength	Begin	End	2008 - 2024
antigen receptor	2009	3.16	**2009**	2015	
therapy	2009	2.81	**2009**	2015	
glioblastoma multiforme	2010	4.16	**2010**	2019	
adjuvant temozolomide	2013	3.82	**2013**	2018	
growth factor receptor	2014	7.1	**2014**	2019	
dendritic cell vaccination	2014	2.56	**2014**	2017	
multiforme	2014	2.56	**2014**	2018	
chimeric antigen receptor	2011	9.66	**2015**	2019	
antitumor activity	2012	5.02	**2015**	2017	
cancer stem cells	2017	4.53	**2017**	2021	
b cell	2017	4.14	**2017**	2019	
tumor infiltrating lymphocytes	2017	2.98	**2017**	2020	
in vivo	2018	3.32	**2018**	2019	
adoptive immunotherapy	2009	3.92	**2019**	2020	
cancer regression	2013	3.1	**2019**	2020	
heterogeneity	2020	3.55	**2020**	2021	
recognition	2014	2.54	**2021**	2022	
radiotherapy	2013	3.49	**2022**	2024	
solid tumors	2020	3.49	**2022**	2024	
efficacy	2008	2.79	**2022**	2024	

Figure 8. Top 20 keywords with the strongest citation bursts.

production of interferon-γ (IFN-γ) by CAR-T cells and upregulated stress ligands targeted by CAR-T cells, thereby enhancing their antitumor efficacy.[29] Smith et al. (2019) demonstrated synergistic effects between CAR-T cells and radiation therapy,[30] while Sabbagh et al. (2021) showed how radiation could enhance CAR-T cell infiltration through blood-brain barrier modulation.[31] In addition, studies have shown that the dose and fractionation schedule of radiotherapy are crucial for the efficacy of combined treatment. Both low-dose (<2 Gy per fraction) and high-dose (>2 Gy per fraction) radiotherapy have been proven to enhance the efficacy of CAR-T cells, but the optimal dose and fractionation regimen still require further investigation.[32,33]

Clinical translation and delivery strategies

Cluster 2 comprised 34 items centered on clinical translation and delivery strategies. This cluster focused on practical implementation challenges, particularly regarding the blood-brain barrier and treatment protocols. O'Rourke et al. (2017) provided crucial insights through their EGFRvIII directed CAR-T cell trial,[20] while Majzner et al. (2022) reported promising results targeting GD2 in diffuse midline gliomas.[22] The results of several studies have shown that the accumulation of CAR-T cells in tumors of patients with glioblastoma is not satisfactory after intravenous injection. In contrast, the efficacy of intravenous CAR-T cells in the treatment of brain metastases from other solid tumors is often remarkable, because brain metastases are usually multifocal and the blood-brain barrier is often disrupted, whereas GBMs are mostly primary tumors, and early disruption of the blood-brain barrier is not obvious.[34,35] Recent work by Agosti et al. (2024) comprehensively reviewed molecular targets and treatment strategies, highlighting emerging approaches for improving delivery and efficacy.[6] Delivery challenges remain a central focus, as indicated by keywords like "blood-brain-barrier" and "central-nervous-system." In GBM, the immunosuppressive microenvironment and tumor physical barriers can affect CAR-T cell spreading and mobility, limiting CAR-T cell delivery and tumor infiltration.[8] A recent study showed that high intra-tumor pressure in the solid tumor microenvironment limits penetration of cell therapy drugs and poses a barrier to drug delivery. Using pressure-assisted drug delivery (PEDD) technology with CAR-T cells, investigators increased cell permeability and persistence within the tumor and increased the concentration of CAR-T cells within the tumor.[36] Additionally a variety of strategies have been proposed to address the transportation of CAR T cells. One strategy is to add chemokine receptor expression to CAR-T cells that bind to and act on chemokines derived from the target tumor.[37] Another strategy is to inject CAR-T cells into the site of the tumor itself. For example HER2-specific CAR-T cells administered intracranially and intratumorally showed superior antitumor a ctivity to intravenous administration and complete tumor regression.[38] Low levels of tumor antigen expression and significant tumor heterogeneity similarly increase the risk of antigen escape and the development of therapeutic resistance, which in turn increases the difficulty of CAR-T cell therapy. The development of CAR-T cells targeting multiple antigens is a viable approach to reduce the risk of antigen escape.[39]

Broader immunotherapy applications

Cluster 3 included 18 items highlighting connections between glioblastoma specific approaches and broader immunotherapy applications. These studies analyzed the use of CAR-T therapy in glioma alongside other cancers, providing broader insights into CAR-T therapy. Yang et al. (2019) demonstrated the importance of understanding basic immune mechanisms through their work on NKG2D CAR-T cells,[40] while Grosser et al. (2019) explored synergies with checkpoint inhibition.[41] Recent studies have expanded our understanding of immune interactions. Liang et al. (2023) reviewed progress in combination therapies,[42] while Singh et al. (2023) detailed advances in CAR design and engineering.[5] There are multiple combination therapy strategies in the treatment of GBM, and the therapeutic efficacy of these strategies should be considered in the first place. In addition to radiotherapy, CAR-T cell therapy is also combined with immune checkpoint inhibitors, chemotherapeutic agents, and oncolytic viruses to enhance anti-tumor effects.[43] The combination of these agents with immune checkpoint inhibitors has been shown to overcome the immunosuppressive characteristics of the TME and enhance the persistence of CAR-T cells. Chemotherapy has been demonstrated to reduce tumor burden, increase immune cell infiltration, and enhance immune response by releasing damage-associated molecular patterns. Oncolytic viruses have been shown to directly infect and kill tumor cells while releasing tumor-associated antigen, thereby enhancing the targeting ability of CAR-T cells. To improve the efficacy of CAR-T cells in solid tumors, there is ongoing research and development of CAR-T cells with enhanced binding affinity for the scFv domain and the capacity to secrete cytokines.[44,45] The use of CRISPR/Cas9 to target specific genes in CAR-T cells has been demonstrated to improve resistance to immunosuppressive signals, thereby maintaining the activity of CAR-T cells within an immunosuppressive TME.[46,47] The inclusion of terms related to other cancers suggests valuable cross-disease learning opportunities, as discussed in Wei et al.'s (2024) analysis of bispecific antibodies in cancer immunotherapy.[48] Presently, numerous clinical trials are underway assessing the efficacy of combining radiotherapy with CAR-T cell therapy for the treatment of solid tumors, which prioritize the analysis of the safety and efficacy of the treatment with a concurrent emphasis on the optimization of the therapeutic regimen to ensure the attainment of optimal clinical outcomes.[49]

Evolution of research hotspots and frontier trends

The temporal evolution of these research clusters reveals a distinct progression in the field of CAR-T therapy for glioblastoma. Early research (2008–2015) focused predominantly on fundamental mechanistic studies, as evidenced by the citation bursts for "antigen receptor" (strength 3.16, 2009–2015) and "therapy" (strength 2.81, 2009–2015). During this period, pivotal studies established the foundational understanding of CAR-T cell biology and basic mechanisms. Fesnak et al. (2016)

provided a comprehensive review of early CAR engineering principles and challenges in their seminal Nature Reviews Cancer paper.[21] The groundbreaking work by Brown et al. (2016) in the New England Journal of Medicine demonstrated the first successful regression of glioblastoma using IL13Rα2-targeted CAR-T cells, establishing proof-of-concept for this approach.[10]

The field then progressed through an intermediate phase (2015–2019) focused on optimizing CAR designs and understanding resistance mechanisms, marked by citation bursts in "chimeric antigen receptor" (strength 9.66, 2015–2019) and "antitumor activity" (strength 5.02, 2015–2017). O'Rourke et al. (2017) made significant contributions during this period, revealing mechanisms of antigen loss and adaptive resistance in their Science Translational Medicine study.[20] Jackson et al. (2019) further elucidated key resistance mechanisms in their Nature Immunology review, providing crucial insights for subsequent therapeutic developments.[25]

More recently (2020–2024), research has shifted decisively toward clinical implementation and combination approaches. This is evidenced by recent citation bursts in "radiotherapy" (strength 3.49, 2022–2024), "solid tumors" (strength 3.49, 2022–2024), and "efficacy" (strength 2.79, 2022–2024). Sabbagh et al. (2021) demonstrated how radiation therapy could enhance CAR-T cell infiltration through blood-brain barrier modulation.[31] Majzner et al. (2022) reported promising results from combining GD2-targeted CAR-T cells with existing treatment modalities in Nature.[22] Liang et al. (2023) comprehensively reviewed various combination strategies, highlighting synergistic effects between CAR-T cells and conventional therapies.[42]

The latest research trends show increasing focus on personalized approaches and treatment optimization. Levstek et al. (2024) proposed novel biomarkers for predicting CAR-T therapy outcomes,[50] while Sadowski et al. (2024) outlined modern therapeutic approaches emphasizing patient stratification.[4] Agosti et al. (2024) provided the most recent comprehensive review of molecular targets and treatment strategies, highlighting emerging directions in combination therapy approaches.[6]

Key challenges for CAR-T therapies

Although CAR-T therapies have made some progress in overcoming the problems of CAR-T cell tumor infiltration, poor auto-cellular function, and poor persistence in vivo,[51,52] there are still many challenges to be faced when using CAR-T cells in the clinic for the treatment of GBM. Fortunately, research targeting these aspects is increasing year by year and making better progress.[53]

Tumor cells have antigenic heterogeneity, which prevents tumor cells from expressing the same antigen targeted by the CAR. It is difficult to find the optimal target antigen that is both tumor-specific and homogeneous when using CAR-T therapy to treat glioblastoma.[54] For example, in a human clinical trial of CAR-T cells with mutant EGFRvIII in GBM in 2017, EGFRvIII-negative tumors appeared, which affected the therapeutic effect.[20] In addition, antigen loss often occurs during treatment, which greatly affects the therapeutic efficacy of CAR-T therapy. Leyuan Ma et al. promoted robust host CD4 and CD8 T-cell responses to non-CAR-associated tumor antigens through in vivo restimulation of a vaccine that activates CAR in lymph nodes. This novel vaccine enables control of antigenically heterogeneous tumors and inhibits tumor recurrence.[54] Hyrenius-Wittsten et al. successfully addressed the antigenic heterogeneity of tumor cells by synthesizing synNotch-CAR T cells targeting GBM antigens.[55]

CAR-T cells have to overcome the complex tumor microenvironment, including extracellular matrix alterations, immunosuppressive cells, myeloid-derived suppressor cells, and tumor-associated macrophages, in the treatment of GBM.[56] The complex tumor microenvironment often limits tumor killing by CAR-T cells, and targeting immunosuppressive cells in the tumor microenvironment may enhance the efficacy of CAR-T cell therapy.Katharina et al. attracted innate immune cells to regulate and remodel the tumor microenvironment by combining constitutive CAR expression with nuclear factor-driven transgene expression in inducible activated T cells.[57]

As CAR-T therapy activates the body's immune system to release large amounts of cytokines such as IFN-γ, IL-1, and IL-6, which may cause damage to the central nervous system and even cytokine release syndrome.[58] Jatiani's team successfully reduced the risk of death associated with CRS by constructing CAR-T cells that can secrete IL-1 R antagonists.[59] In addition CAR-T therapies of GBM may have many other types of toxicity in actual treatment, including targeting toxicity, neurotoxicity, allergic reactions. Different therapeutic strategies c an be used in treatment according to the actual situation.[60]

Currently, tumor antigen expression heterogeneity, immunosuppressive tumor microenvironment and CAR-T therapy toxicity are the major challenges hindering the efficacy of CAR-T therapy in GBM. Further studies are needed to improve CAR-T efficacy and reduce its toxicity. However, it is believed that combining CAR-T cell therapy with chemotherapy, radiotherapy, or other immunotherapies has the potential to improve the efficacy of CAR-T cell therapy in the future.

Strengths and limitations

This study presents several distinct advantages. First, we conducted a systematic analysis of the research landscape concerning glioblastoma and CAR-T immunotherapy using bibliometric methods for the first time, thereby providing comprehensive guidance for scholars in this domain. Second, we utilized three complementary bibliometric tools concurrently, which ensures an objective and thorough analysis of the data. Finally, our bibliometric approach offers a more nuanced understanding of research hotspots and frontiers compared to traditional review methods. Nevertheless, this study is not without its limitations. First, our data were sourced exclusively from the WoSCC database, potentially omitting relevant studies indexed in other databases. Second, we restricted our analysis to English-language publications, which may have resulted in an underestimation of contributions from non-English-speaking regions.

Conclusions

This bibliometric analysis elucidates the rapid evolution and contemporary state of research pertaining to glioblastoma and CAR-T immunotherapy over the past 17 years. The field is delineated into three distinct phases of investigation, progressing from foundational mechanisms to clinical applications. This change in the different phases of the study suggests that CAR – T therapies have great clinical translational potential. Current research hotspots underscore the importance of combination therapy approaches, the enhancement of treatment efficacy, and the development of strategies to surmount challenges associated with solid tumors. The emergence of keywords such as "radiotherapy," "solid tumors," and "efficacy" as recent burst terms indicates a burgeoning interest in multimodal treatment strategies and their clinical outcomes. This will provide guidance to more researchers in the future on the trends and future prospects in this field. With the increasing number of CAR-T therapies being researched, CAR-T immunotherapy is expected to have a golden age in the coming years and benefit more patients suffering from glioblastoma.

Acknowledgments

Zhong Wang and Zhouqing Chen were the principal investigators. Zhaoming Song designed the study and developed the analysis plan; Chen Yang, Jinyu Gu and Yanao Guo analyzed the data; Yun Xie, Zhaoming Song, Ruisi Qu and Xun Nong contributed to the writing of the article. Zhaoming Song, Chen Yang and Jinyu Gu revised the manuscript and polished the language. All authors read and approved the final submitted paper.

Disclosure statement

Zhaoming Song, Chen Yang, Jingyu Gu, Ruisi Qu, Yun Xie, Yanao Guo, Xun Nong, Zhouqing Chen, Zhong Wang have nothing to disclose.

Author contributions

CRediT: **Zhaoming Song:** Data curation, Writing – original draft, Writing – review & editing; **Chen Yang:** Formal analysis, Writing – original draft, Writing – review & editing; **Jingyu Gu:** Data curation, Software, Validation; **Ruisi Qu:** Data curation, Methodology, Writing – original draft; **Yun Xie:** Software, Writing – review & editing; **Yanao Guo:** Methodology, Writing – review & editing; **Zhouqing Chen:** Conceptualization, Writing – review & editing; **Zhong Wang:** Conceptualization, Writing – review & editing.

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Consent for publication

Nothing to report.

Ethics approval and consent to participate

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Funding

The author(s) reported there is no funding associated with the work featured in this article.

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