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The 15-year bibliometric landscape of glioblastoma vaccines: Emergence of combinatorial immunotherapy

Zhi Long and Kun Liu

Department of Neurosurgery, The Second People's Hospital of Hunan Province (Brain Hospital of Hunan Province), Clinical Medical School, Hunan University of Chinese Medicine, Changsha, China

ABSTRACT

Despite the persistently poor prognosis of glioblastoma (GBM), research into novel immunotherapies, particularly tumor vaccines, has flourished, evolving into a highly active and interdisciplinary field. Through a bibliometric analysis of 1,096 relevant publications from 2010 to 2025, this study systematically maps the intellectual structure, collaborative networks, and thematic evolution of this domain. The analysis reveals a significant paradigm shift: the research focus has transitioned from early antigen-specific vaccine development toward the comprehensive modulation of the immunosuppressive tumor microenvironment. This shift is evidenced by in-depth investigations into combination immunotherapies (e.g., with immune checkpoint inhibitors), advanced delivery technologies designed to overcome the blood-brain barrier (such as focused ultrasound and biomimetic nanocarriers), and innovative platforms including oncolytic viruses and stem cell-based systems. Overall, over the past 15 y, the field has evolved from strategies centered on unilateral immune activation toward integrated, synergistic approaches aimed at counteracting systemic immunosuppression. Future breakthroughs are anticipated to depend on refining personalized neoantigen-targeting strategies and optimizing multimodal combination therapeutic regimens.

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Introduction

Glioblastoma (GBM), designated as a grade IV malignancy in the World Health Organization (WHO) classification of central nervous system tumors, remains the most aggressive and lethal primary brain tumor in adults. Despite incremental advances in surgical techniques, radiotherapy protocols, and adjuvant chemotherapy – particularly the use of temozolomide – the prognosis for patients with GBM remains dismal. The median overall survival ranges from 12 to 15 months with standard treatment, and fewer than 6.8% of patients survive beyond five years.[1] The disease is characterized by rapid progression, diffuse infiltration into surrounding brain tissue, and an almost universal tendency toward recurrence, even after multimodal therapy. These features underscore GBM's status as one of the most formidable challenges in modern oncology.

Over the past 15 y, there has been a paradigm shift in GBM research, moving from conventional cytoreductive strategies toward immunomodulatory approaches. Among emerging immunotherapies, therapeutic vaccination has gained increasing attention due to its potential to induce durable, tumor-specific immune responses. Unlike chemotherapy or radiation, which exert nonspecific cytotoxic effects, cancer vaccines aim to harness the patient's own immune system to recognize and eliminate malignant cells in a targeted manner. This active immunization strategy may be particularly valuable in preventing recurrence by establishing long-term immune surveillance.[2] The evolution of GBM vaccine platforms has been marked by significant technological diversification: from synthetic peptide vaccines targeting oncogenic mutations such as EGFRvIII (e.g., Rindopepimut), to autologous dendritic cell-based vaccines (e.g., DCVax-L), and more recently, mRNA-based and nanocarrier-delivered vaccines. These developments reflect a broader trend toward personalized, multi-antigenic, and immunologically enhanced therapeutic designs.[3,4]

CONTACT Kun Liu 330256@hnucm.edu.cn Department of Neurosurgery, The Second People's Hospital of Hunan Province (Brain Hospital of Hunan Province), Clinical Medical School, Hunan University of Chinese Medicine, No. 427, Section 3, Furong Middle Road, Yuhua District, Changsha, Hunan 410007, China.

Nonetheless, clinical translation of GBM vaccines has been hindered by multiple biological and physiological barriers. Tumor heterogeneity – both inter- and intra-patient – complicates target antigen selection, while the immunosuppressive tumor microenvironment (TME), enriched with regulatory T cells, myeloid-derived suppressor cells, and immunomodulatory cytokines, dampens effector immune responses. Furthermore, the presence of the blood-brain barrier (BBB) limits the trafficking of immune cells and therapeutic agents into the central nervous system.[5] These factors collectively contribute to the limited efficacy observed in late-stage clinical trials.[6] For instance, Rindopepimut, a peptide vaccine targeting EGFRvIII, demonstrated promising results in phase II studies (ACT III trial), with a reported median survival of 21.8 months. However, it failed to improve overall survival in the subsequent phase III ACT IV trial, leading to the discontinuation of its development.[7] Such setbacks highlight the limitations of single-epitope targeting and emphasize the need for multi-targeted, adaptable, and combinatorial immunotherapeutic strategies.

The scientific output in the field of GBM vaccine research has grown substantially in recent years. According to bibliographic data, approximately 1,096 peer-reviewed articles on GBM vaccines were published globally between 2010 and 2025. This expanding body of literature spans diverse vaccine platforms, antigen selection methods, delivery systems, and combination regimens. While this growth reflects heightened research interest and technological innovation, it also poses challenges related to information overload and knowledge fragmentation. The field is increasingly specialized, with studies scattered across immunology, neuro-oncology, bioengineering, and computational biology, often without sufficient integration. Traditional narrative reviews, though insightful, are inherently limited in scope and may overlook emerging patterns due to subjective selection biases.

Bibliometric analysis offers a systematic, quantitative approach to map the intellectual and structural landscape of a scientific domain. By analyzing publication outputs, citation networks, co-authorship patterns, and keyword evolution, this method enables objective assessment of research trends, identification of influential contributors, and visualization of collaborative networks. In the context of GBM vaccines, bibliometrics can help disentangle complex knowledge structures, reveal dominant research themes, and trace the trajectory of technological innovation.[8] Although bibliometric studies have been conducted on broader topics in neuro-oncology and cancer immunotherapy, no comprehensive analysis has specifically focused on the global research landscape of GBM vaccines.

It is pertinent to address the novelty and distinct contributions of the present analysis in light of our team's prior bibliometric work. Our previous study provided a panoramic, two-decade overview of the entire glioblastoma immunotherapy landscape, encompassing diverse modalities such as immune checkpoint inhibitors, CAR-T therapy, and vaccines. In contrast, the current manuscript performs a targeted, deep-dive analysis specifically into the therapeutic vaccine subfield. This focused scope constitutes its primary advancement, enabling a granular examination of vaccine-specific intellectual evolution, platform diversification, and unique challenges that were beyond the resolution of the broader prior analysis. Methodologically, this study utilizes a novel and updated dataset (2010–2025) that captures the most dynamic and transformative period for cancer vaccine technology. The analysis goes beyond descriptive mapping to identify and elaborate a significant paradigm shift: from early antigen-specific vaccine development toward strategies centered on comprehensive tumor microenvironment modulation and rational combinatorial immunotherapy. Consequently, the conclusions offer a specialized and forward-looking roadmap tailored for the vaccine research community, delineating future directions that hinge on overcoming tumor heterogeneity, reversing immunosuppression, and breaching the blood-brain barrier through synergistic combinations. Therefore, this work represents a necessary and significant specialization, providing refined insights and strategic guidance distinct from and complementary to our earlier panoramic review.

This study presents a bibliometric evaluation of glioblastoma vaccine research from 2010 to 2025, based on data extracted from major scientific databases. The analysis aims to assess the global research output and its temporal evolution, identifying key contributing countries, institutions, and individual researchers who have shaped the field. International collaboration patterns are mapped to reveal the structure of scientific networks and the dynamics of cross-border knowledge exchange. Through keyword co-occurrence and cluster analysis, we explore the thematic evolution of research focus, uncovering emerging hotspots and conceptual shifts over time. Finally, the study interprets these findings in the context of current challenges and opportunities, offering insights into future research trajectories. By providing a comprehensive, data-driven synthesis of the field, this work seeks to support evidence-based decision-making among researchers, funding bodies, and health policy stakeholders, ultimately promoting strategic investment and interdisciplinary innovation in the advancement of GBM immunotherapy.

Materials and methods

Data collection

A systematic literature search was conducted on July 28, 2025, using the Web of Science Core Collection (WoSCC) expanded database (Thomson Reuters, New York, USA). The search query was: TS = ("Glioblastoma" OR "GBM") AND TS = ("Vaccin*"), where TS denotes topic search (title, abstract, author keywords, and Keywords Plus). The publication date range was set from July 28, 2010, to July 28, 2025.

Inclusion and exclusion criteria: Only original research articles and review articles published in English were included. Conference abstracts, letters, editorials, corrections, and news items were excluded. No restrictions were applied regarding geographic region or institution.

A total of 1,394 records were initially identified. After screening titles and abstracts, 251 records were excluded (non-relevant topics, duplicate publications, or non-English language), yielding 1,096 publications for final analysis. The literature screening process is illustrated in Figure 1.

Data analysis

Visualization analysis and knowledge map construction were performed using CiteSpace (version 5.8.R1) and VOSviewer (Leiden University, Leiden, The Netherlands). CiteSpace was primarily applied for keyword co-occurrence analysis and burst detection of co-cited references. The parameter configuration for CiteSpace included a time span from 2010 to 2025, one-year time slices,

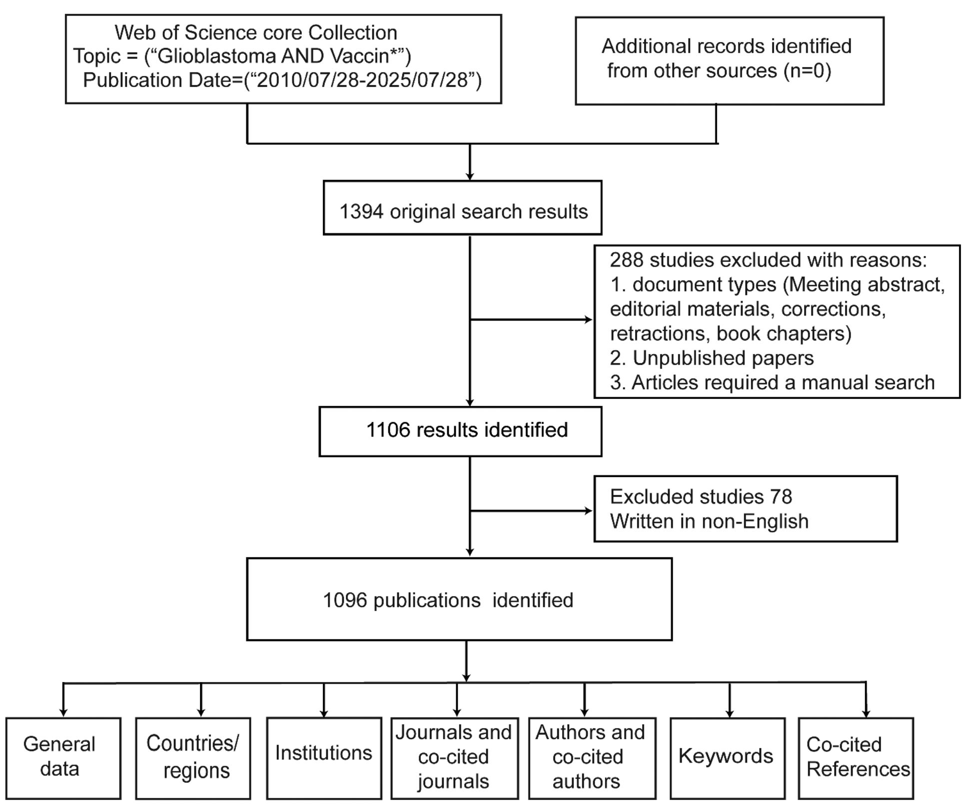

Figure 1. Flowchart of the data collection and bibliometric analysis process. The workflow outlines the steps from initial database search and screening to final data analysis using bibliometric tools.

a g-index selection criterion (k = 25), and no pruning of the merged networks. In the co-citation network generated, cluster labels were derived from index terms using the log-likelihood ratio (LLR) algorithm.

VOSviewer was utilized as a complementary bibliometric tool to generate and visually explore knowledge maps based on network data. In the resulting VOSviewer network visualizations, nodes are colored according to their cluster affiliation, and their size is proportional to the frequency of keyword co-occurrence. The association strength between nodes is quantified by the Total Link Strength (TLS) metric, which is visually represented by the width of the connecting links. Based on its capacity for generating lucid and interpretable cluster visualizations, VOSviewer was selected to perform cluster analyses of countries, institutions, journals, authors, references, and keywords.

Results

Global publication output and trend analysis

As shown in Figure 2, between July 28, 2010, and July 28, 2025, a total of 1,096 publications on GBM increased from 17 in 2010 to 121 in 2024 (611.76% growth), reflecting sustained research momentum. The average annual growth rate was 15.05%, with the most rapid expansion occurring after 2020, coinciding with the rise of personalized immunotherapy.

National contributions to global research

A total of 47 countries participated in GBM vaccine research during the 15-y period. Table 1 highlights the top 10 most prolific nations. The United States led with 511 publications (29,015 citations), followed by China (185 publications, 5,567 citations) and Germany (112 publications, 7,783 citations). In terms of average citations per paper, Germany ranked highest (69.5), followed by the U.S. (56.8) and Italy (55.2), whereas China's average was lower (30.1), suggesting room for improvement in research impact.

Using VOSviewer, we visualized the international collaboration network (Figure 3), revealing 20 countries interconnected through research partnerships. The U.S., China, and Germany emerged as central hubs, with the U.S. exhibiting the strongest collaboration intensity (total link strength [TLS] = 6,691), underscoring its leadership. Notably, Sino-American collaboration (TLS = 1,142) demonstrated the highest interconnectivity, reflecting their strategic research alliance.

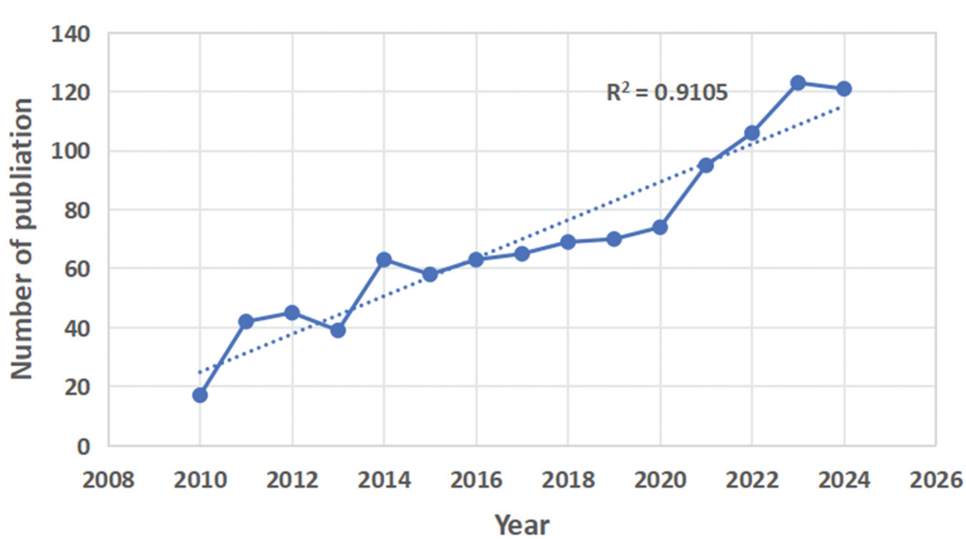

Figure 2. Annual distribution of publications in the field over time. The trend reflects the cumulative growth of research output from the earliest recorded publication year to the present.

Table 1. The top 10 countries according to total publications during 2010–2025.

Rank	Country	Number of publications	Proportion(%)	Total citations	Total link strength
1	The USA	511	46.6%	29015	6691
2	China	185	16.8%	5567	2689
3	Germany	112	10.2%	7783	2550
4	Italy	62	5.6%	2221	1089
5	Japan	57	5.2%	2502	816
6	England	45	4.1%	3747	1283
7	Switzerland	44	4.0%	4419	1338
8	Belgium	43	3.9%	2733	769
9	Russia	34	%	461	325
10	Iran	28	%	393	570

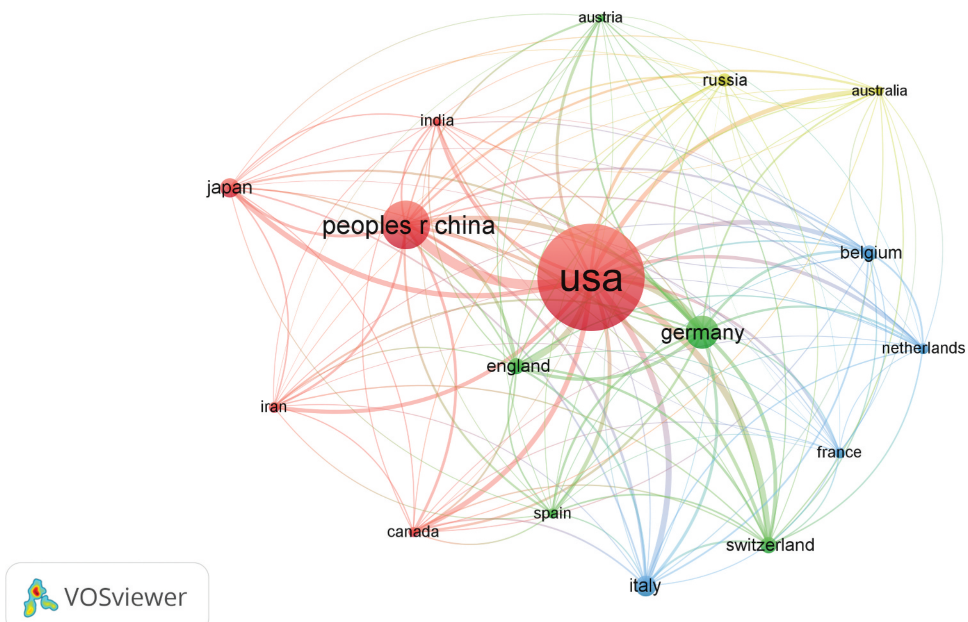

Figure 3. Country-level collaboration network map generated using VOSviewer. Node size is proportional to the number of publications by each country. Link thickness between nodes represents the strength of collaborative efforts.

Institutional productivity and collaboration

Table 2 lists the top 10 institutions by publication count. Duke University ranked first with 64 publications (5,250 citations), followed by Harvard Medical School (37 publications, 2,010 citations) and the University of California, San Francisco (33 publications, 3,862 citations). Most top institutions were U.S.-based. A collaboration network of 15 institutions (Figure 4) revealed Duke University as the most interconnected node (TLS = 64), highlighting its pivotal role in fostering academic partnerships.

Table 2. The top 10 most productive institutions between 2010 and 2025.

Rank	The name of institution	Publications	Citations	Location
1	Duke University	64	5250	The USA
2	Harvard Med Sch	37	2010	The USA
3	University Calif San Francisco	33	3862	The USA
4	German Canc Res Ctr	29	2940	The USA
5	Northwestern University	29	1385	The USA
6	University Florida	29	1187	The USA
7	Univ Calif Los Angeles	26	1379	
8	Mayo Clin	26	910	The USA
9	Stanford University	25	1838	German
10	Dana Farber Canc Inst	24	2149	The USA

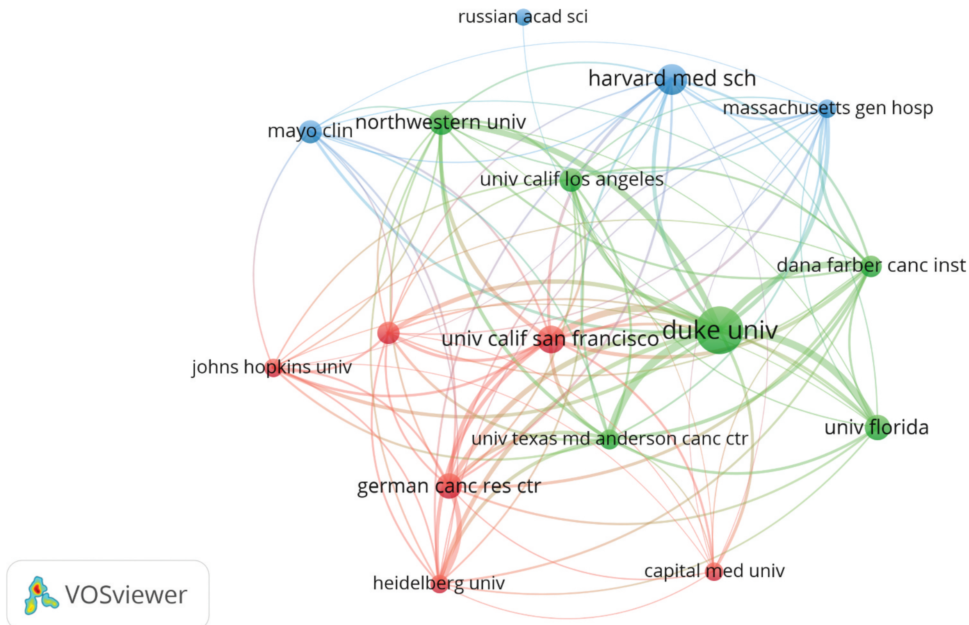

Figure 4. Institutional collaboration network mapped via VOSviewer. Node size corresponds to the number of publications affiliated with each institution. The thickness of the links indicates the intensity of collaborative research activities.

Leading journals and co-cited journals

VOSviewer visualization (Figure 5) mapped the collaboration network among the 16 most prolific journals in the field (Figure 5(a)), reflecting active knowledge exchange and co-publication patterns, while also illustrating the co-citation network of the 16 most influential journals (Figure 5(b)), which reveals the core body of literature that jointly shapes the intellectual foundation of glioblastoma vaccine research.

Table 3 summarizes the top 10 journals by output and co-citation frequency. Cancers (Basel) (IF = 4.4, 2024) published the highest volume (49 papers), followed by Frontiers in Immunology (IF = 5.9, 2024; 42 papers) and Clinical Cancer Research (IF = 5.19, 2024; 36 papers). Co-citation analysis revealed Clinical Cancer Research as the most cited (4,666 co-citations), followed by Neuro-Oncology (IF = 5.27, 2024; 4559 co-citations) and Cancer Research (IF = 16.60, 2024; 3,280 co-citations), emphasizing their academic authority.

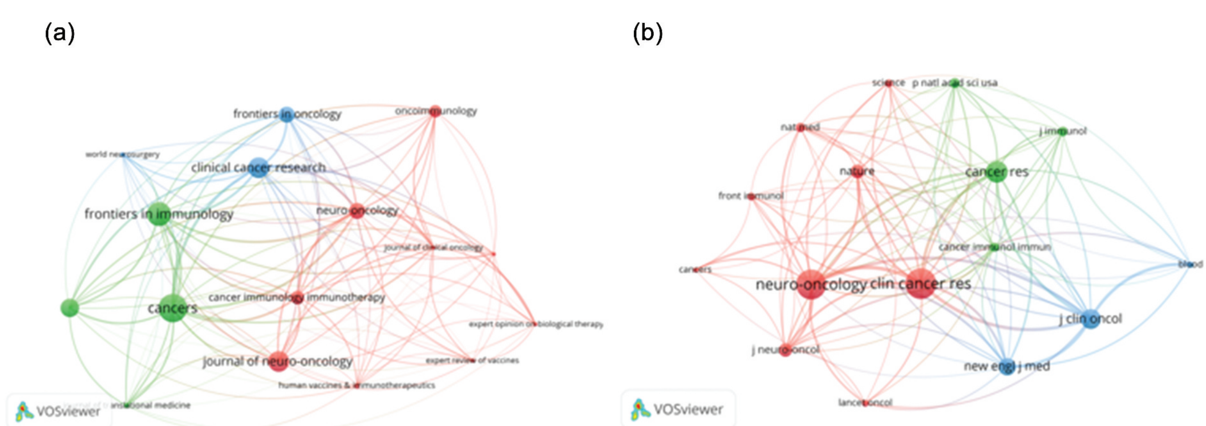

Figure 5. Journal collaboration network constructed using VOSviewer. Node size reflects the number of publications associated with each journal, while link width represents the strength of co-occurrence or collaborative ties between journals.

Table 3. Top 10 prolific journals and co-cited journals on glioblastoma vaccine research from 2010 to 2025.

Rank	Journal	Publications	Citations	IF	Co-cited journal	Co-citations	IF
1	Cancers	49	949	4.4	Clin Cancer Research	4666	5.19
2	Frontiers in Immunology	42	1304	5.9	Neuro-Oncology	4559	5.27
3	Clinical Cancer Research	36	3327	5.19	Cancer Research	3280	16.60
4	Journal of Neuro-Oncology	36	1153	1.59	J Clin Oncology	3069	5.19
5	International Journal of Molecular Sciences	32	628	4.9	New Engl J Med	2634	78.50
6	Neuro-Oncology	28	2426	5.27	Nature	2148	48.50
7	Frontiers in Oncology	28	704	1.61	J Neuro-Oncology	2059	1.59
8	Cancer Immunology Immunotherapy	24	1518	2.78	P Natl Acad Sci USA	1514	9.1
9	Oncoimmunology	22	995	3.03	J Immunology	1470	5.42
10	Immunotherapy	13	381	1.21	Nat Med	1458	49.2

Abbreviation: IF, impact factor.

Prominent authors and co-cited scholars

Over the 15-y period, 5,984 authors contributed to GBM vaccine research. Table 4 ranks the top 10 authors by publication count and co-citation frequency, representing influential figures and collaborators. Sampson JH was the most prolific (39 papers), followed by Mitchell DA (26 papers) and Reardon DA (25 papers). Co-citation analysis identified Stupp R (919 citations), Sampson JH (710 citations), and Reardon DA (546 citations) as the most impactful scholars. VOSviewer visualized author collaboration (Figure 6(a)), while co-citation networks (Figure 6(b)) highlighted 15 authors with ≥219 co-citations. Notably, Stupp R and Reardon DA exhibited the strongest collaboration (TLS = 838).

Table 4. Top 10 prolific authors and co-cited authors on glioblastoma vaccine research from 2010 to 2025.

Rank	Author	Publications	Citations	Country	Citations/paper	Co-citedauthor	Co-citations	Country
1	Sampson, JH	39	4549	USA	116	Stupp, R	919	USA
2	Mitchell, DA	26	2745	USA	105.5	Sampson, JH	710	USA
3	Reardon, DA	25	2811	USA	112.4	Reardon, DA	546	USA
4	Okada, H	22	1640	USA	74.5	Liau, LM	487	USA
5	Lim, M	22	2488	USA	113.0	Weller, M	448	Switzerland
6	Heimberger, AB	15	1781	USA	118.7	Okada, H	395	USA
7	Weller, M	14	2504	Switzerland	178.8	Brown, CE	367	USA
8	Finocchiaro, G	14	1144	Italy	81.7	Wen, PY	320	USA
9	Van Gool, SW	13	853	Belgium	65.6	Heimberger, AB	300	USA
10	Chiocca,E.A	13	1015	USA	78.0	Prins, RM	285	USA

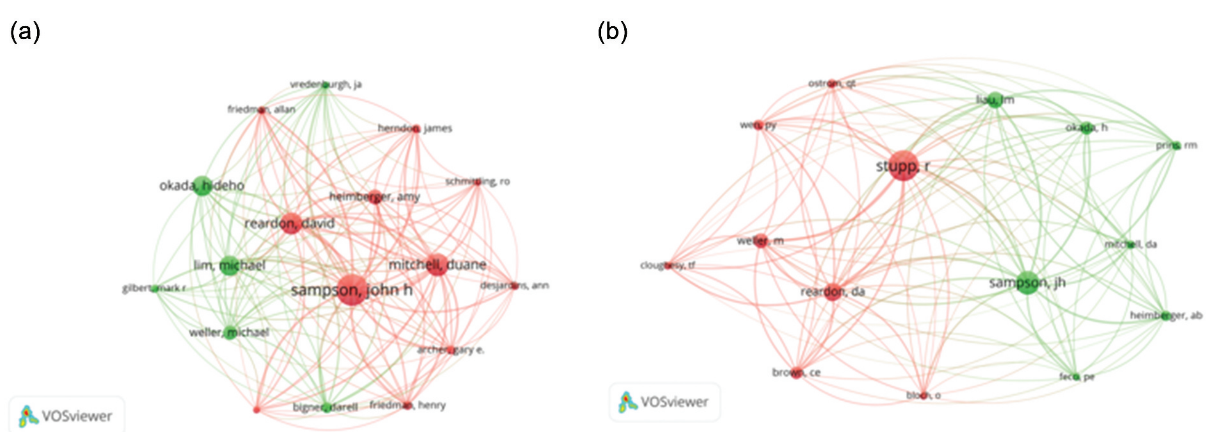

Figure 6. Author-level collaboration networks visualized using VOSviewer: (a) co-authorship network among leading authors; (b) network of coauthors. Node size indicates publication output, and link thickness reflects the frequency or strength of collaboration.

Highly co-cited literature

Co-cited publications reflect foundational studies frequently referenced together. Table 5 lists the top 10 co-cited works. The most seminal was Stupp R et al.'s 2005 New England Journal of Medicine study (n = 445)[9] on radiotherapy plus temozolomide for GBM, establishing the standard of care. Sampson JH et al.'s 2010 Journal of Clinical Oncology paper on EGFRvIII vaccination (n = 225)[10] and Weller M et al.'s 2017 ACT IV trial on rindopepimut (n = 188)[11] followed. VOSviewer mapped the top 15 co-cited works (Figure 7(a)), while CiteSpace identified 25 core references with citation bursts (strength: 17.36–41.18; Figure 7(b)). Notably, Liau LM et al.'s 2023 DCVax-L trial exhibited the highest burst strength (30.88), underscoring its recent impact and signaling a shift toward personalized vaccine strategies.

High-frequency keyword analysis

Keywords reflect research hotspots and emerging trends. VOSviewer's co-occurrence network (Figure 8(a)) identified dominant themes clustered into three major groups: (1) vaccine platforms (peptide, DC, mRNA); (2) TME and immunosuppression (TME, MDSC, Treg, immune checkpoint); and (3) combination strategies and delivery technologies (combination therapy, checkpoint inhibitors, focused ultrasound, BBB)., while CiteSpaceburst detection (Figure 8(b)) revealed that terms such as "tumor microenvironment," "double-blind," "blood-brain barrier," "oncolytic viruses," and "stem cells" have experienced the strongest citation bursts since 2020, collectively mapping the field's evolving focus toward overcoming barriers to vaccine efficacy.

Table 5. Top 10 co-cited reference according to total publications on glioblastoma vaccine research during 2010 to 2025.

Rank	Co-cited reference	Co-citations
1	Stupp R, 2005, New Engl J Med, v352, p987, doi 10.1056/nejmoa043330	445
2	Sampson JH, 2010, J Clin Oncol, v28, p4722, doi 10.1200/jco.2010.28.6963	225
3	Weller M, 2017, Lancet Oncol, v18, p1373, doi 10.1016/s1470-2045(17)30517-x	188
4	Stupp R, 2009, Lancet Oncol, v10, p459, doi 10.1016/s1470-2045(09)70025–7	184
5	Liau LM, 2005, Clin Cancer Res, v11, p5515, doi 10.1158/1078–0432.ccr-05–0464	183
6	Phuphanich S, 2013, Cancer Immunol Immun, v62, p125, doi 10.1007/s00262-012–1319-0	152
7	Liau LM, 2018, J Transl Med, v16, doi 10.1186/s12967-018–1507-6	152
8	O'Rourke DM, 2017, Sci Transl Med, v9, doi 10.1126/scitranslmed.aaa0984	148
9	Brown CE, 2016, New Engl J Med, v375, p2561, doi 10.1056/nejmoa1610497	144
10	Okada H, 2011, J Clin Oncol, v29, p330, doi 10.1200/jco.2010.30.7744	140

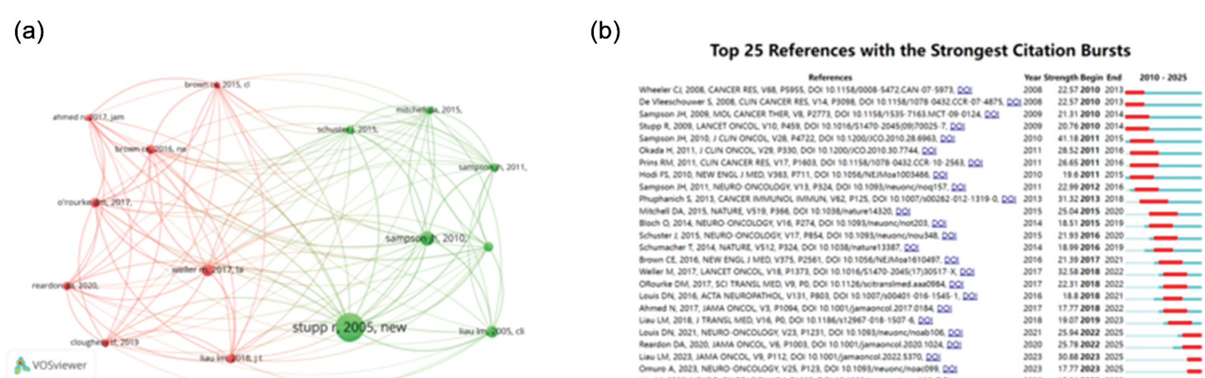

Figure 7. Co-citation analysis of references: (a) network visualization of co-cited references generated by VOSviewer. Node size corresponds to citation frequency, with larger nodes indicating highly cited references. Node color reflects clustering based on citation proximity, indicating thematic similarity. (b) Top 25 references with the strongest citation bursts. Red bars denote burst duration, and burst intensity reflects the significance and temporal impact of a reference within the research domain.

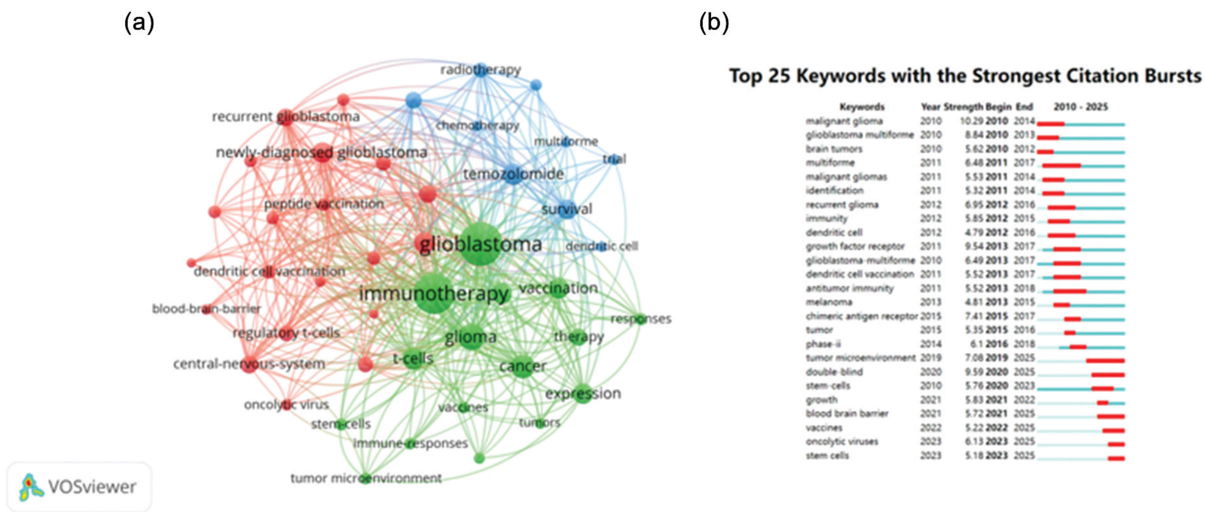

Figure 8. Author keyword co-occurrence analysis: (a) network visualization of frequently occurring author keywords using VOSviewer. Node size represents keyword frequency, with larger nodes indicating higher occurrence. Clustering and color similarity reflect conceptual or thematic proximity. (b) Top 25 keywords with the strongest citation bursts. Red bars indicate burst duration, and burst intensity reflects the relative importance and emerging trends of keywords in the field.

Discussion

This study systematically analyzed 1,096 publications related to GBM vaccine research from 2010 to 2025 using bibliometric methods, revealing trends in research output, contributions of nations/institutions, distribution of core research forces, and the evolution of research hotspots.

First, the steady increase in annual publication numbers over the past 15 y underscores GBM vaccine development as a vital direction in tumor therapeutics, maintaining consistent research momentum and dynamic growth. This trend may be attributed to the poor clinical prognosis of GBM patients, the urgent demand for novel therapeutic strategies, and breakthroughs in immunotherapy advancements in recent years.

Analysis of national and institutional contributions highlighted an uneven global distribution of research efforts. The United States demonstrated undisputed leadership in this field, with the highest publication count, total citations, and overall link strength in international collaboration networks. Notably, the exceptionally robust collaboration between China and the U.S. (total link strength = 1,142) formed a central axis of global scientific cooperation, emphasizing the critical role of large-scale international partnerships in advancing cutting-edge research. Additionally, leading institutions such as Duke University and Harvard Medical School, predominantly based in the U.S., further consolidated the nation's dominance. This advantage likely stems from a well-established biomedical innovation ecosystem, substantial funding, and a strong foundation for interdisciplinary collaboration.

Assessment of journals and authors provided insights into the field's knowledge sources and academic influence. High-output journals like Cancers and Frontiers in Immunology serve as key platforms for disseminating research findings, while highly cited journals such as Clinical Cancer Research, Neuro-Oncology, and Cancer Research represent foundational theoretical pillars and authoritative knowledge repositories, shaping subsequent research trajectories. Similarly, highly productive authors (e.g., Sampson, J. H.) and co-cited scholars (e.g., Stupp, R) identified key contributors, with their collaborative networks (e.g., Stupp, R and Reardon, D.A.) reflecting the reliance of high-impact research on stable, efficient scientific teams.

Analysis of co-cited literature delineated the knowledge base evolution in GBM vaccine research. Stupp et al.'s 2005 temozolomide chemoradiotherapy protocol, established as the GBM standard of care, remains the benchmark for evaluating novel therapies, including vaccines.[9] Studies by Sampson, J.H. and Weller, M. on EGFRvIII-targeted vaccines (e.g., Rindopepimut) marked a pivotal transition from conceptual frameworks to clinical validation of antigen-specific active immunotherapy.[10,11] Notably, emerging citation bursts, such as those on autologous tumor lysate-loaded dendritic cell vaccines (DCVax-L), indicate significant academic impact and suggest personalized vaccine strategies may represent a promising future direction.[12]

High-frequency keyword analysis offers a panoramic view of the knowledge architecture and evolutionary trajectories within a specific research domain. By integrating VOSviewer and CiteSpace, this study not only identifies core research themes in GBM vaccine development but also captures dynamic frontiers and emerging trends.

The immunosuppressive tumor microenvironment (TME) of glioblastoma (GBM) is not a static backdrop but a functional ecosystem that actively shapes therapeutic responses and drives immune escape. Successful vaccine strategies must therefore move beyond simple antigen presentation to systematically decode and remodel this hostile landscape.

Conventional perspectives primarily attribute GBM immunosuppression to myeloid cells such as MDSCs and GAMs. These cells directly impair effector T cell function and promote their apoptosis by secreting factors like TGF-β and IL-10, and by expressing arginase-1 (Arg-1) to deplete arginine in the microenvironment.[13,14] However, recent single-cell and spatial transcriptomic studies reveal that this suppression is highly organized and hierarchical.[15]

First, spatial heterogeneity constitutes the first line of defense. Specific "immune-shielded" niches exist within the GBM TME. For instance, the ischemic and hypoxic core not only induces the expression of VEGF and various immunosuppressive factors via HIF-1α but also actively recruits and polarizes TAMs into subsets with enhanced suppressive capabilities. These cells form tight physical interactions with tumor cells and directly inhibit infiltrating T cells through checkpoint molecules like PD-L1/PD-1 and CD80/CTLA-4.[16] Second, the dynamic remodeling of non-cellular components forms a second line of defense. Extracellular matrix (ECM) components secreted by GBM and stromal cells, such as tenascin-C and hyaluronan, not only create a physical barrier to T cell infiltration but also transmit pro-survival signals directly to tumor cells via integrin signaling and induce T cell dysfunction.[17]

More critically, immunosuppression operates as a "relay" process. An initial vaccine-induced immune response may recruit and activate cytotoxic T lymphocytes (CTLs). However, as these CTLs attempt to infiltrate the tumor parenchyma, they encounter sequential interception by distinct mechanisms: first, suppression by VISTA-expressing myeloid cells in the perivascular space[18]; followed by interception by adenosine-high regulatory T cells (Tregs) at the tumor margin; ultimately leading to terminal exhaustion in the core due to nutrient deprivation and persistent inhibitory signals.[19] Therefore, any effective intervention must disrupt this continuous inhibitory chain rather than targeting a single component.

The groundbreaking discovery by Gao et al. has brought the B cell lineage to the forefront of GBM immunotherapy discussions, revealing an alarming tumor-promoting axis. The enrichment of plasma cells in the GSC niche and their activation of the PI3K-AKT-mTOR signaling pathway in GSCs via secreted IgG binding to FcγRIIA presents a dual challenge to current therapeutic paradigms.[20]

First, it exposes the "double-edged sword" nature of humoral immunity in GBM. While vaccines traditionally aim to elicit protective antibody responses, this study suggests that in specific microenvironments – particularly niches enriched with GSCs – these antibodies can be "hijacked" by the tumor. They may be converted into signals that sustain stemness, promote therapy resistance, and drive recurrence.[20] This implies that future vaccine design requires meticulous evaluation of the induced antibody response, potentially avoiding epitopes or antibody isotypes that might activate FcγRIIA signaling. Second, the study raises a direct caution regarding widely used immune checkpoint inhibitors (ICIs). Most clinical anti-PD-1/PD-L1 antibodies are of the IgG type. When their Fc regions engage FcγRIIA on GSCs, they may not only fail to relieve immunosuppression but could directly stimulate the proliferation of these stem cells.[20] This provides a plausible mechanistic explanation for the phenomenon of hyperprogression observed in some patients following ICI therapy. This finding strongly advocates for the priority use of Fc-silenced or engineered ICI antibodies (e.g., IgG4 subclass switching, Fc amino acid point mutations) in GBM combination therapies to eliminate potential pro-tumor side effects while preserving pure checkpoint blockade function.[21]

Given the aforementioned complexity, combination therapy has evolved from an option to a necessity. However, successful combination is not a simple additive process but should be based on a deep understanding of complementary mechanisms of action, enabling coordinated intervention at multiple steps of the cancer-immunity cycle.

The phase II trial by Ahluwalia et al. demonstrated the potential of SurVaxM combined with TMZ.[22] The synergistic mechanism likely extends beyond the conventional view of "vaccine activating immunity, chemotherapy killing tumor." Low-dose, metronomic TMZ administration has been shown to selectively deplete circulating Tregs, reducing the systemic immunosuppressive burden and creating a more favorable environment for vaccine-activated effector T cells. However, given TMZ's concurrent lymphocytotoxic effects, inappropriate timing could inadvertently damage newly activated vaccine-specific T cell clones. Therefore, optimizing the sequence – for instance, initiating the vaccine to prime an immune response before employing metronomic TMZ for maintenance and microenvironment modulation – may be a key focus for future research.

Directly targeting MDSCs and TAMs is central to breaking down the TME barrier. Current strategies include: (1) Blocking recruitment: Using CCR2 or CSF-1 R inhibitors to prevent monocyte migration from bone marrow to the tumor[23]; (2) Reprogramming function: Employing CD40 agonist antibodies to revert immunosuppressive M2-like macrophages toward an antigen-presenting and immunostimulatory M1-like phenotype[24]; (3) Depleting populations: Utilizing antibody-drug conjugates (ADCs) targeting specific surface markers. Combining vaccines with these approaches aims to first convert "cold" tumors into "hot" ones, allowing vaccine-induced immune cells to effectively infiltrate and function.

Even with successful systemic immune activation, effector cells and molecules must still cross the blood-brain barrier (BBB) to reach the tumor site. Ultrasound combined with microbubbles (e.g., the SonoCloud device) can temporarily and reversibly open the BBB, significantly enhancing the delivery efficiency of vaccine effectors (e.g., antibodies, cytokines, T cells). This technology's safety and feasibility have been validated in clinical trials.[25] Furthermore, post-surgical implantation of vaccine-loaded biocompatible hydrogels into the resection cavity can establish a local "immune micro-factory." This system enables sustained release of antigens and adjuvants, recruiting and activating immune cells in situ to mount a continuous assault on residual disease and the immunosuppressive microenvironment, a strategy demonstrating strong potential in preclinical models.[26]

Double-blind randomized controlled trials (RCTs) represent the gold standard for evaluating the efficacy of therapeutic vaccines in GBM. One of the most recognized phase III RCTs in this field is the ACT IV trial, which investigated the EGFRvIII-targeted peptide vaccine rindopepimut. Despite encouraging outcomes from earlier single-arm studies, this phase III trial failed to demonstrate improved OS, highlighting the limitations of single-antigen vaccines in addressing tumor heterogeneity and antigen escape mechanisms.[11] Another landmark double-blind RCT in GBM immunotherapy is the phase III study evaluating the dendritic cell vaccine DCVax-L. This trial enrolled patients with newly diagnosed GBM who received standard temozolomide chemotherapy and were randomized to either the DCVax-L arm or placebo. The study implemented a rigorous double-blind design to ensure unbiased assessment of therapeutic efficacy. Final results revealed a significant extension of OS in the vaccine-treated group, with long-term follow-up data exhibiting a pronounced "long tail effect," suggesting the induction of durable antitumor immune memory.[27] This trial not only validated the clinical potential of personalized dendritic cell vaccines in GBM treatment but also established high-level evidence for cell-based immunotherapy in solid tumors through its methodologically robust design.

Double-blind randomized controlled trials (RCTs), the gold standard for evaluating therapeutic vaccine efficacy, provide not only evidence of effectiveness but also, through their rigorous design, reveal the inherent conceptual limitations of treatment strategies and pathways for optimization. In the field of GBM vaccines, the contrasting outcomes of the phase III RCTs for ACT IV and DCVax-L serve as an instructive comparative case study, compelling a profound reevaluation of the complex interplay between vaccine antigen strategy, trial design, and disease biology.

The failure of the ACT IV trial represents the systematic defeat of a "single-antigen strategy" against a "highly evolvable and adaptable tumor."[11] Rindopepimut targeted EGFRvIII, a tumor-specific antigen resulting from a gene rearrangement expressed in approximately 20–30% of GBM patients. Encouraging signals from earlier studies obscured a fundamental weakness: EGFRvIII is a clonal, not a pan-clonal, antigen. Under the selective pressure exerted by the vaccine, tumor cells expressing EGFRvIII were eliminated by the immune system. In contrast, tumor cell clones lacking this antigen – whether preexisting or newly emerging via epigenetic silencing or gene loss – gained a proliferative advantage, leading to "immunoediting" and antigen-negative recurrence. This process underscores the dynamic nature of intratumoral heterogeneity in GBM.[28] Deeper analysis suggests that strategies targeting single driver mutation-derived antigens may fail to engage the core cell population sustaining tumor growth – glioblastoma stem cells (GSCs) – which often exhibit distinct antigen expression profiles and possess enhanced immune evasion capabilities.

In contrast, the success of DCVax-L implies a different philosophical approach to overcoming heterogeneity.[12] This vaccine utilizes patient-derived autologous tumor lysate-loaded dendritic cells, constituting an individualized, multi-antigen immunotherapeutic strategy. It contains thousands of unknown tumor-associated antigens and neoantigens, theoretically capable of eliciting a polyclonal T-cell response against multiple tumor clones. This significantly reduces the risk of treatment failure due to the loss of a single antigen. The observed "long-tail effect" – where a subset of patients achieves exceptionally long-term survival – strongly suggests that this multi-target attack may have incidentally triggered truly effective immune surveillance against cancer stem cells or critical clones, enabling profound disease control. This comparison clearly indicates that future antigen selection must shift from "seeking a magic bullet" to "constructing an arsenal of antigenic combinations," or leverage neoantigen prediction technologies to develop genuinely personalized, polyvalent vaccines.[29]

While the double-blind design minimizes bias, the traditional RCT paradigm faces unique challenges when evaluating active immunotherapies like vaccines, necessitating innovation.

First, patient population heterogeneity acts as a "diluent" for efficacy signals. GBM exhibits vast differences at the molecular level (e.g., IDH status, MGMT promoter methylation), within the immune microenvironment ("cold" vs. "hot" tumors), and in tumor antigen repertoire. Applying a vaccine based on a specific antigen (e.g., EGFRvIII) to an unselected patient population (as in ACT IV), or employing a multi-antigen vaccine without considering baseline immune status, inevitably dilutes efficacy by including many patients with low potential for response. Therefore, selecting a "biomarker-enriched population" is not merely an optimization strategy but a necessary prerequisite.[30] Future trials must integrate genomic, transcriptomic, and immune repertoire analyses to identify subgroups most likely to benefit from a specific vaccine's mechanism of action. For instance, for neoantigen vaccines, patients with high tumor mutational burden (TMB) and specific HLA genotypes should be selected.

Second, the choice of endpoint must align with the mechanism of action of immunotherapy. Overall survival (OS), while the gold standard, is significantly confounded by subsequent lines of therapy and may not sensitively capture the delayed clinical benefits characteristic of immunotherapies. The phenomenon observed in the DCVax-L trial – minimal progression-free survival (PFS) advantage but significant OS extension – is a classic example of "dissociated response" in immunotherapy, where initial radiographic progression may reflect immune cell infiltration (pseudoprogression) rather than true tumor growth. Consequently, reliance on PFS alone may mistakenly reject effective therapies.[31] Future trials must explore and validate surrogate endpoints, including: (1) Immunological endpoints: Frequency, functionality (polyfunctionality), and memory phenotype of vaccine-induced antigen-specific T cells. (2) Imaging-based immune endpoints: Utilizing advanced MRI (e.g., perfusion imaging) or PET (e.g., anti-CD8 antibody imaging) to distinguish pseudoprogression from true progression. (3) Dynamic monitoring via liquid biopsy: Monitoring molecular response through circulating tumor DNA (ctDNA), particularly in cerebrospinal fluid, which may change earlier than radiographic findings and correlate strongly with OS.[32]

Glioma stem cells (GSCs) are widely recognized as the central drivers of therapeutic resistance and recurrence in GBM.[33] Their self-renewal capacity, significant intratumoral heterogeneity, and dynamic interactions with TME collectively constitute a robust defensive system. GSCs are not a static cell population; they exhibit a high degree of phenotypic plasticity, enabling them to transition between different molecular subtypes (e.g., mesenchymal and proneural) to adapt to therapeutic pressures and drive tumor evolution.[34] This plasticity implies that vaccines designed against a specific GSC subpopulation or state may fail if the target cells undergo phenotypic switching during treatment – a process accompanied by alterations in antigen expression profiles, known as "immunoediting." Furthermore, GSCs possess intrinsic resistance to conventional radiotherapy and chemotherapy. They frequently overexpress various drug efflux pumps and DNA damage repair proteins, which further shield them from elimination by adjuvant therapies. Consequently, even if a vaccine successfully initiates an immune response, the failure to effectively kill the target GSCs through chemotherapy may prevent the complete eradication of the tumor.

GSCs are far more than passive therapeutic targets; they essentially function as the "master architects" of the TME.[35] First, GSCs are adept at exosome-mediated long-distance communication to systematically reprogram immune cells. For instance, a 2024 study confirmed that exosomes secreted by GSCs carry the long non-coding RNA NEAT1. Upon delivery to tumor-associated macrophages (TAMs), NEAT1 drives TAMs toward an immunosuppressive M2 phenotype by suppressing miR-125a expression and upregulating its target gene STAT3.[36] These "re-educated" M2 macrophages subsequently secrete large amounts of IL-10 and TGF-β, establishing a self-reinforcing, positive feedback loop that continuously amplifies immunosuppression and directly undermines vaccine-elicited T-cell responses. Second, GSCs dominate metabolic competition. Acting as "metabolic sinks," they rapidly consume glucose and glutamine in the TME through vigorous glycolysis and glutaminolysis, leading to nutrient depletion and lactate accumulation, which results in local acidosis.[37] This hostile metabolic milieu is detrimental to infiltrating cytotoxic T lymphocytes (CTLs): glucose shortage impedes their energy acquisition and proliferation, while lactate directly suppresses their cytotoxic function and promotes exhaustion, rendering vaccine-activated effector cells ineffective. Furthermore, GSCs endeavor to construct dual physical and molecular barriers: they tend to enrich in perivascular or hypoxic niches, forming physical immune-sanctuary sites. At the molecular level, GSCs commonly overexpress immune checkpoint molecules such as PD-L1 and CD47.[35] The former directly inhibits T-cell function, while the latter delivers a "don't eat me" signal to macrophages, synergistically suppressing both innate and adaptive immunity. In summary, through the synergy of exosomal communication, metabolic dominance, and physical-molecular barrier establishment, GSCs construct a multi-layered, dynamic immunosuppressive fortress. Any vaccine strategy targeting them must first devise means to breach this complex ecosystem of their own making.

The core challenge and key to developing effective GSC-targeted vaccines lies in identifying ideal tumor antigens – molecules that are stably and highly expressed on GSCs, crucial for maintaining their stemness, and absent or expressed at minimal levels in normal tissues. Reflecting on history, the exploration of traditional targets such as EGFRvIII offers a profound lesson: despite its tumor specificity, the Phase III clinical trial (ACT IV) targeting it ultimately failed. The fundamental reason was the significant intratumoral antigen heterogeneity and therapy-induced antigen loss, exposing the inherent vulnerability of single-target strategies when confronting the dynamic evolution of GSC populations.[11] Another target, IL13Rα2, carries potential safety risks due to its low-level expression in some normal tissues. These challenges have driven research toward identifying new targets with greater prevalence and functional criticality. In this context, the discovery of the emerging target PTPRZ1 marks a significant advance. Research by Chih et al. demonstrates that the receptor-type tyrosine-protein phosphatase Z1 (PTPRZ1) is widely and stably overexpressed in GBM tissues and GSCs, yet its expression is highly restricted in adult normal brain tissue.[38] Their preclinical studies confirmed that a PTPRZ1-targeting peptide vaccine can induce potent antigen-specific T-cell responses and effectively suppress tumor growth. More notably, the study successfully cloned a PTPRZ1-recognizing T-cell receptor (TCR) from a post-immunotherapy patient and constructed TCR-T cells capable of specifically killing GSCs. This provides direct proof-of-principle for developing personalized cell-based vaccines targeting this antigen. Looking ahead, to thoroughly overcome single-antigen escape, antigen strategies for vaccines must evolve toward multiplexing or complete personalization. This entails developing "multivalent vaccines" that simultaneously target PTPRZ1 along with other GSC-associated antigens (e.g., BIRC5/Survivin), or employing whole-exome sequencing to screen for neoantigens derived from GSC-specific mutations to create fully individualized "neoantigen vaccines."

Facing the complex defensive system constituted by GSCs and their multilayered, dynamic barriers, monotherapeutic vaccination strategies are unlikely to succeed. Future transformative progress will necessarily depend on intelligent combination therapy – the construction of a coordinated regimen integrating precision targeting, comprehensive TME remodeling, and innovative delivery platforms. The core rationale of this strategy is "synergistic barrier disruption."

The foremost pillar of this approach is the rational combination of vaccines with TME-remodeling agents. While multivalent or neoantigen vaccines provide "precision-guided munitions," it is imperative to concurrently dismantle immunosuppression and improve the "battlefield conditions." This includes: (1) combining with immune checkpoint inhibitors (e.g., anti-PD-1 antibodies) to block inhibitory signals on T cells; (2) using

CSF-1 R inhibitors or CD47-blocking antibodies to deplete or reprogram immunosuppressive myeloid cells[23,39]; and (3) applying metabolic modulators targeting pathways like lactate transport or indoleamine 2,3-dioxygenase (IDO) to alleviate the nutrient-deprived and metabolically suppressed state of the TME, with targeting the TGF-β signaling axis being a key direction for reversing immunosuppression.[15] Additionally, combining vaccines with other modalities like oncolytic viruses and overcoming associated resistance mechanisms is a vital strategy for enhancing efficacy.[40]

The second pillar lies in innovative delivery technologies and administration strategies to ensure therapeutic forces effectively penetrate the blood-brain barrier (BBB) and reach the central nervous system. This involves: (1) implanting biodegradable hydrogels loaded with vaccine components and immune adjuvants into the post-surgical resection cavity to create a local, sustained-release "immune micro-factory"[41]; and (2) utilizing magnetic resonance-guided focused ultrasound combined with microbubbles to achieve transient, reversible, and spatially precise BBB opening, thereby significantly enhancing the delivery efficiency of systemically administered vaccine components, antibodies, or adoptive T cells to the tumor site.[25]

In summary, only through such a multimodal, sequential combination strategy – precisely attacking GSCs while systematically deconstructing the immunosuppressive niche they depend on – can we ultimately overcome GBM's therapeutic resistance and translate the potential of therapeutic vaccines into long-term survival benefits for patients.

The development of effective vaccine therapies for GBM is fundamentally challenged by two interrelated barriers: the restrictive physiology of the blood-brain barrier (BBB) and the profoundly immunosuppressive TME. The BBB, with its tight junction complexes and active efflux pumps, acts as a formidable physical and biochemical filter, severely limiting the intracranial delivery of vaccine components and the subsequent infiltration of peripherally activated effector T cells.[42] Even when immune priming is achieved systemically, the "cold" nature of the GBM TME – characterized by poor antigen presentation, an abundance of regulatory immune cells, and metabolically suppressive conditions – often abrogates the effector phase of the anti-tumor response, leading to a discouraging disconnect between peripheral immunity and intracranial efficacy.

In response, research has pivoted toward two synergistic strategies: engineering more potent immunogens and developing intelligent delivery platforms capable of BBB penetration. While peptide and dendritic cell (DC) vaccines have established a foundation of safety and some clinical benefit, their efficacy remains limited by the aforementioned barriers.[43] Emerging nanovaccine platforms offer a promising solution by integrating antigen and adjuvant into a single, engineered particle. Notably, biomimetic strategies, such as those utilizing tumor cell membrane-derived vesicles, present a broad antigenic repertoire while enhancing homing to tumor sites. Crucially, innovative administration routes, such as intranasal delivery, can bypass the BBB entirely via the olfactory pathway, enabling direct brain delivery and potent TME remodeling, as demonstrated in preclinical models where such approaches reversed M2 macrophage polarization and enhanced $CD8^+$ T cell infiltration.[44] Complementary to these active vaccination platforms, technologies aimed at transiently disrupting the BBB, most notably MRI-guided focused ultrasound (MRgFUS), are entering clinical trials to enhance the delivery of co-administered therapeutics, including immune checkpoint inhibitors.[45]

Despite these advances, significant translational hurdles remain. The heterogeneity of GBM necessitates personalized antigen selection, yet the timeline and cost associated with neoantigen identification and custom vaccine production are substantial. Furthermore, the long-term safety profiles of novel nanocarriers and physical BBB opening techniques require thorough investigation. Our findings and those of others suggest that the future of GBM immunotherapy lies not in a single modality but in rational combination strategies. The most promising clinical path likely involves a multi-pronged attack: a personalized vaccine platform (e.g., mRNA or nanovaccine) delivered via a BBB-penetrating method (e.g., intranasal or carrier-mediated), combined with agents that counteract the local immunosuppressive TME, such as PD-1/PD-L1 checkpoint blockade. Continued research must focus on refining target antigen selection, optimizing the spatiotemporal control of immune activation, and validating robust immunological biomarkers to guide clinical application. Ultimately, overcoming the unique challenges of the brain is essential to unlocking the full potential of immunotherapy for this devastating disease.

The therapeutic landscape for GBM is undergoing a paradigm shift, moving from monotherapies toward rational, multimodal combinations aimed at overcoming the intertwined challenges of inter- and intra-tumoral heterogeneity, a profoundly immunosuppressive TME, and the formidable BBB.[46] The synergistic integration of cancer vaccines with oncolytic virotherapy exemplifies this next-generation approach. Oncolytic viruses (OVs), such as herpes simplex virus type 1 (oHSV-1), serve a dual function: they act as *in situ* vaccines by mediating immunogenic cell death and releasing a broad antigenic repertoire, while simultaneously reprogramming the "cold" TME. This reprogramming is achieved through the induction of type I interferons and recruitment of innate immune cells, thereby creating an inflamed, lymphocyte-infiltrated milieu that is prerequisite for effective adaptive immunity. Recent mechanistic work by Guo et al. provides a critical advancement for this strategy by identifying BRD9 as a key epigenetic driver of GBM resistance to oHSV-1. Their demonstration that BRD9 inhibition enhances viral replication and antitumor efficacy offers a compelling pharmacological strategy to precondition tumors, thereby optimizing the "antigenic soil" for subsequent vaccination, particularly against therapy-resistant glioblastoma stem cells.[40]

Parallel to advances in virotherapy, the field of personalized neoantigen vaccination has matured to provide the necessary precision. These vaccines are designed to elicit T-cell responses against patient-specific somatic mutations, directly addressing the issue of clonal heterogeneity. The clinical feasibility and immunogenicity of this approach have been robustly demonstrated. Keskin et al. provided foundational proof-of-concept, showing that personalized neoantigen vaccines could induce polyfunctional, tumor-infiltrating, mutation-specific T-cell responses in newly diagnosed GBM patients.[29] Building upon this, long-term follow-up data from larger cohorts, such as that reported by Latzer et al., confirm the durable immunogenicity and a significant survival benefit in patients mounting robust, multi-antigen immune responses.[47] These findings underscore that the breadth and quality of the neoantigen-specific T-cell repertoire are critical biomarkers of clinical efficacy.

The logical convergence of these platforms – using OVs to prime the TME and release antigens, followed by neoantigen vaccines to boost and focus the immune response – represents a highly rational combinatorial strategy. However, its translation faces several structured challenges. First, determining the optimal therapeutic sequence is non-trivial, as the dynamic interplay between viral kinetics and vaccine-induced clonal expansion requires empirical optimization in preclinical models.[44] Second, effective CNS delivery and antigen presentation remain paramount. Innovative delivery solutions, such as convection-enhanced delivery (CED) of OVs or implantable biomaterial scaffolds for sustained local vaccine release, are actively being explored to bypass the BBB and ensure high intratumoral drug levels.[44] Finally, even a successfully initiated immune response may be extinguished by persistent immunosuppression. Therefore, the most potent regimen will likely be a triple-combination therapy, integrating oncolytic virotherapy, personalized vaccination, and immune checkpoint blockade to simultaneously ignite, educate, and sustain the anti-glioma immune response.[48]

In conclusion, the future of GBM therapy lies in the strategic assembly of complementary modalities. The synergy between oncolytic viruses (as broad activators and TME remodelers) and personalized neoantigen vaccines (as precision-targeting systems) provides a powerful blueprint. Success will depend on meticulously addressing the challenges of treatment sequencing, CNS biodistribution, and immunosuppression through iterative translational research and biomarker-driven clinical trial designs.

In recent years, research into GBM immunotherapy has evolved from simplistic immune-activation strategies toward sophisticated, multi-dimensional intervention paradigms. While ICIs have achieved remarkable success in various solid tumors, their efficacy in GBM has been disappointing, a failure largely attributed to GBM's unique characteristics: an immunologically "cold" TME, profound inter- and intra-tumoral heterogeneity, and the physiological barrier posed by the BBB, which restricts the trafficking of both drugs and immune effector cells. In this challenging landscape, therapeutic vaccines have emerged as a particularly promising modality due to their capacity to induce durable, tumor-specific T-cell responses, offering the potential for long-term immunological memory and surveillance. The field of GBM immunotherapy is currently undergoing several critical paradigm shifts. First, it is moving from single-target to multi-target and personalized combinations; the clinical failure of single-antigen vaccines like Rindopepimut underscores the inability of narrowly focused strategies to counter GBM's profound clonal heterogeneity and immunoediting capabilities,[11] whereas multi-antigen approaches, such as the tumor lysate-loaded dendritic cell vaccine DCVax-L, have demonstrated more durable clinical benefits by eliciting a polyclonal T-cell response against a diverse array of tumor clones.[12] Second, the focus is shifting from mere immune activation to active immune microenvironment remodeling, as the GBM TME is not a passive backdrop but an active, multi-layered defense system that suppresses effector T cells through metabolic competition, expression of immune checkpoints, and recruitment of immunosuppressive cells[13,14]; consequently, future vaccine strategies must be rationally combined with TME-remodeling agents such as CSF-1 R inhibitors,[23] CD40 agonists,[24] or metabolic modulators to effectively "fertile the soil" for vaccine-induced immune responses. Third, the field is progressing from relying on systemic immunity toward developing localized delivery strategies, as the BBB remains a formidable obstacle that limits the infiltration of peripherally activated immune cells; to overcome this, innovative approaches such as implanting vaccine-eluting biocompatible hydrogels into the resection cavity,[41] intranasal administration that bypasses the BBB entirely,[44] and MRI-guided focused ultrasound for transient BBB disruption are at the forefront of current research.[25] A systematic evaluation of combination vaccine immunotherapy reveals that such approaches have transitioned from optional strategies to an inevitable necessity for GBM, with the core principle being to synergistically target multiple steps of the cancer-immunity cycle. The combination of vaccines with immune checkpoint inhibitors operates through a mechanism where vaccines prime and expand tumor-specific T cells while ICIs reinvigorate exhausted T cells within the TME; although pre-clinical models and early-phase trials suggest enhanced efficacy, challenges include immune-related adverse events and the limited effect in immunologically "cold" tumors, as well as the recent discovery that unmodified IgG antibodies may inadvertently promote GSC growth, advocating for the use of Fc-silenced ICI antibodies in GBM.[20,21] The combination of vaccines with oncolytic viruses offers a powerful synergistic mechanism wherein viruses like oHSV-1 induce immunogenic cell death to release a broad antigen repertoire while simultaneously remodeling the "cold" TME into a "hot," inflamed state, thereby creating an ideal milieu for a subsequent vaccine to amplify the antigen-specific T-cell response; representative research by Guo et al. on combining oHSV-1 with a BRD9 inhibitor provides a compelling roadmap for optimizing this approach,[40] though challenges such as neutralizing antibodies against viral vectors and the need for optimal sequencing remain. The combination of vaccines with chemotherapy or radiotherapy leverages mechanisms where metronomic temozolomide can selectively deplete regulatory T cells and radiotherapy can induce immunogenic cell death, with the Phase IIa trial of SurVaxM combined with adjuvant TMZ demonstrating feasibility[22]; however, the lymphocytotoxic effects of these modalities necessitate precise scheduling to achieve synergy without antagonism. Finally, the combination of vaccines with TME-targeted agents such as CSF-1 R inhibitors,[23] CD40 agonists,[24] and anti-CD47 antibodies aims to dismantle the physical and cellular barriers of the TME,[39] creating a permissive environment for vaccine-induced T cells to infiltrate and function effectively, positioning these agents as key components of future "triple combination" therapies.

Looking toward future directions, the evolution of GBM immunotherapy points toward the development of systemically integrated, multi-modal therapeutic platforms rather than simplistic drug combinations. Key components of this integrated approach will include precision antigen identification through single-cell sequencing and TCR screening to develop truly personalized vaccines targeting clonal neoantigens and stable GSC-associated antigens like PTPRZ1[29,38,47]; intelligent delivery systems such as implantable scaffolds,[41] biomimetic nanocarriers, and intranasal administration to achieve high,[44] sustained drug concentrations within the tumor while bypassing the BBB; dynamic immunomonitoring integrating longitudinal analysis of circulating tumor DNA in cerebrospinal fluid and T-cell receptor sequencing to provide real-time feedback on treatment efficacy[32]; and sequential regimen optimization toward rationally sequenced protocols such as "TME preconditioning followed by OV priming, then vaccine boosting, and finally ICI maintenance" to maximize the depth and durability of the anti-tumor immune response.[40,48] In summary, GBM immunotherapy is at a critical juncture, transitioning from empirical combinations toward mechanistically driven, system-level integration. As a core component of this evolving paradigm, combination vaccine therapy must achieve breakthroughs across multiple dimensions including antigen design, delivery technology, TME modulation, and treatment sequencing. Ultimately, only through sustained multidisciplinary collaboration and the implementation of precision medicine-guided clinical trial designs can we fully translate the potential of immunotherapy into a meaningful and durable survival benefit for patients with this devastating disease.

Limitations

This study has several limitations. First, the data were sourced exclusively from the WoSCC, which may not fully capture regionally specialized or non-indexed publications. Second, bibliometric methodologies inherently focus on macro-level trends, and their inability to dissect specific technical pathways or clinical outcomes necessitates integration with complementary methodologies such as systematic reviews or meta-analyses. Third, recent high-impact publications may be underrepresented due to citation lag, as newly emerging studies require time to accumulate citations and demonstrate their full academic influence.

Conclusion

Through a comprehensive bibliometric analysis of GBM vaccine research over the past 15 y, this study draws the following conclusions: First, the field is experiencing a dynamic and sustained growth trajectory, with steady global research output reflecting persistent scientific and clinical commitment to addressing this formidable challenge. Second, research efforts are characterized by a U.S.-led core with deep international collaboration involving China, Germany, and other nations. This collaborative framework plays a pivotal role in accelerating knowledge innovation and translational advancements. Third, the knowledge foundation of the field has evolved from foundational studies establishing standard therapies to clinical trials exploring targeted vaccines, culminating in the current era of personalized vaccines and combination strategies. Research hotspots demonstrate a clear evolution from "vaccine design" to "systemic immune modulation." Future breakthroughs hinge on overcoming tumor heterogeneity, reversing immunosuppressive microenvironments, and surmounting physiological barriers such as the BBB. Fourth, diverse vaccine platforms (e.g., peptide vaccines, dendritic cell [DC] vaccines, mRNA vaccines) each present unique advantages and challenges. Emerging trends emphasize personalized strategies, multi-target approaches, and synergistic integration with immunotherapies and conventional therapies.

In summary, these macro-level insights provide researchers with a strategic roadmap to navigate the field, identify key literature and collaboration opportunities, and prioritize innovation directions. As precision medicine and biotechnology advance, vaccine therapies are poised to play an increasingly central role in comprehensive GBM treatment paradigms, ultimately offering renewed hope for improved patient outcomes.

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CRediT: **Zhi Long:** Writing – original draft; **Kun Liu:** Writing – review & editing.

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Notes on contributor

Liu Kun, Director Physician, Department of Neurosurgery, Hunan Provincial Brain Hospital, Hunan Province. Graduated from Xiangya School of Medicine, Central South University. Specializes in cerebrovascular and spinal vascular diseases, as well as hemorrhagic and ischemic disorders, including aneurysms, vascular malformations, cavernous hemangiomas, arteriovenous fistulas, intracerebral hemorrhage, moyamoya disease, carotid artery stenosis, cerebral infarction, and related conditions.

Data availability statement

In this study, data sharing is not applicable as no new data were generated. The datasets utilized originated from publicly available resources: https://webofscience-clarivate-cn-s-225.libdb.csu.edu.cn/wos/woscc/summary.

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