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ORIGINAL RESEARCH

Oncolytic Virotherapy for Glioma: A Bibliometric Roadmap for Multidisciplinary Clinical and Research Strategies

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Background: Glioblastoma (GBM) remains the most lethal primary brain tumor with a dismal prognosis despite standard therapies. Oncolytic viruses (OVs), which selectively destroy cancer cells and stimulate anti-tumor immunity, have emerged as a promising therapeutic strategy. This study aims to systematically map the global research landscape, knowledge structure, and evolutionary trends of OV therapy for gliomas.

Methods: Publications from 2009 to 2025 were retrieved from the Web of Science Core Collection (WOSCC). Bibliometric analysis and knowledge mapping were conducted using CiteSpace and RStudio to analyze collaboration networks, co-citation patterns, and keyword evolution.

Results: A total of 559 publications were analyzed. The annual output has grown exponentially since 2020, with the USA and China being the most productive countries. A clear paradigm shift was identified, moving from early research focused on direct oncolysis by viral vectors like Herpes Simplex Virus to a current emphasis on immuno-virotherapy. Recent hotspots are dominated by keywords such as immunotherapy, combination, tumor microenvironment, and T-cells, indicating a research trajectory towards complex, synergistic treatment strategies. Harvard University and Brigham and Women's Hospital are the leading institutions in this field.

Conclusion: The research field of oncolytic virotherapy for gliomas is rapidly advancing, with a clear evolution towards sophisticated combination immunotherapies. This analysis provides a comprehensive roadmap of the field's knowledge base and identifies key future directions, including overcoming delivery barriers and developing personalized treatment protocols, to accelerate the clinical translation of this promising therapy.

Keywords: oncolytic viruses, gliomas, bibliometrics, research trends, CiteSpace

Introduction

Gliomas are the most common and aggressive primary tumors of the central nervous system, with glioblastoma (GBM) having an extremely poor prognosis.[1] Although the current "Stupp" standard of care (surgery combined with chemoradiotherapy) has made efforts to extend patient survival,[2] the median overall survival remains around 15 months, and the five-year survival rate is less than 10%, highlighting the profound limitations of current therapies.[3] The therapeutic dilemma of GBM stems from its high heterogeneity, diffuse infiltration, and general resistance to conventional therapies.[4] Therefore, developing innovative strategies to break through the treatment bottleneck has become an urgent priority in the field of neuro-oncology. In this context, oncolytic virotherapy, as an emerging biotherapeutic paradigm, has shown immense potential.[5] Oncolytic viruses (OVs) are therapeutic agents genetically engineered to selectively replicate within and destroy tumor cells—a feat of engineering built upon the foundational understanding of viral morphology and ultrastructure provided by techniques like transmission electron microscopy (TEM).[6] These viruses function via a unique dual mechanism of action: direct viral oncolysis and potent immune activation. This dual action can effectively transform an immunosuppressive "cold" tumor microenvironment into an immune-activated "hot" one, thereby initiating a durable anti-tumor immune response and offering a novel perspective for treating immunogenically "cold" GBM.[7,8]

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As research has deepened, the academic community has recognized that although oncolytic virus monotherapy has demonstrated safety in early clinical trials, its efficacy is limited and insufficient to overcome the complex immunosuppressive network of GBM.[9,10] This recognition resonates with insights gained from other viral infections. For instance, the recent Coronavirus disease 2019 (COVID-19) pandemic has profoundly illustrated how a viral infection can trigger complex systemic pathophysiological responses, with effects extending far beyond the primary organ through intricate interactions with the host immune system.[11] This global health crisis has significantly elevated the focus on virology and immunology within both public and scientific spheres, providing a new lens through which to understand virus-host interactions and indirectly fueling the enthusiasm for research into viral-based therapeutics like OVs. Consequently, the research focus in the field has clearly shifted towards combination therapy strategies, aiming to maximize anti-tumor effects through synergistic multi-target action.[12] Among these, the combination of OV and immune checkpoint inhibitors (ICIs) has become the most prominent research direction, as the immune-"heating" effect of the former can create the prerequisite for the efficacy of the latter.[13] In recent years, with the approval of the genetically engineered hs (HSV) G47Δ (Teserpaturev) in Japan for the treatment of recurrent GBM, and its demonstration of an unprecedented one-year survival rate in a Phase II clinical trial, a powerful momentum has been injected into the entire field. This marks a critical turning point for oncolytic virus therapy, transitioning from theoretical exploration to clinical practice.[14–16]

On this critical scientific issue, research is growing exponentially worldwide, posing significant challenges to the systematic integration of knowledge and the accurate identification of research frontiers. While traditional systematic reviews and meta-analyses have unique advantages in evidence synthesis, bibliometric analysis, which uses quantitative indicators such as citation networks and keyword co-occurrence, can more systematically reveal the knowledge base, collaboration patterns, and evolutionary trajectory of a field.[17] This large-scale scientific knowledge mapping technology not only provides researchers with a panoramic view of the field but also helps identify knowledge gaps and formulate strategic plans for innovation.[18] It is noteworthy that while some bibliometric studies have analyzed the overall trends in the oncolytic virus field or its application in the broader context of central nervous system tumors,[19,20] a dedicated and comprehensive bibliometric study on the critical intersecting paradigm of "OV" and "glioma" is still lacking. This knowledge gap needs to be filled. Therefore, this study employs bibliometric and scientific knowledge mapping methods to identify the core research forces, interdisciplinary trends, and potential breakthrough directions in this field through a systematic analysis of relevant literature from the past 16 years, aiming to provide a clear theoretical framework and technological roadmap for the future translation of basic research into clinical applications.

Materials and Methods

Search Strategy

To ensure the reliability and authority of the data, this study selected the Web of Science Core Collection (WOSCC) database as the sole data source. WOSCC is renowned for its high-quality peer-reviewed literature and comprehensive citation indexing system, and its powerful analytical functions provide key support for citation network research.[21]

The search query for this study was constructed as follows: TS=((glioblastoma* OR "glioblastoma multiform*" OR "malignant glioma" OR "brain cancer*" OR gliosarcoma* OR spongioblastoma* OR astrocytoma* OR "astrocytic tumor*" OR "astrocytic glioma*" OR "astrocyte tumor*" OR oligodendroglioma* OR "oligodendroglial tumor*" OR GBM OR LGG)) AND TS=("Oncolytic Virotherapy" OR "Oncolytic Virotherapies" OR "Oncolytic Virus Therapy" OR "Oncolytic Virus Therapies" OR "Oncolytic Viruses" OR "Oncolytic Virus").

Inclusion and Exclusion Criteria

This study established clear inclusion and exclusion criteria. The inclusion criteria were: (1) peer-reviewed research articles or review articles published in English; (2) studies that explicitly explored the application of OV in glioma or related pathological mechanisms; (3) a publication date range from January 1, 2009, to May 9, 2025.

The exclusion criteria included: (1) non-peer-reviewed materials (eg, preprints, conference abstracts, letters, book chapters, data papers); (2) retracted publications; (3) studies whose topics were not directly related to OV or glioma; (4) to ensure consistency in data processing, non-English literature was excluded.

The literature screening was conducted independently by two researchers, and any disputed items were resolved through discussion and consensus.

Data Extraction

Bibliometric parameters extracted from the qualifying literature included: article title, publication year, author information (name, country/region, institution), citation frequency, source journal, publication type, author affiliations, keywords, and reference list.

Bibliometric Analysis

The extracted data were imported into CiteSpace (version 6.3.R1 Advanced), Microsoft Excel, RStudio (version 4.4.2), and an online bibliometric analysis platform (http://bibliometric.com/) for data processing and network visualization. CiteSpace served as the core analytical tool, employing visualized bibliometric methods to reveal the underlying knowledge within scientific literature. It generates scientific knowledge maps that intuitively display the structure and distribution of scientific knowledge.[22] These maps cover various types, including institutional/national collaboration networks, reference co-citation clusters, burst detection graphs, keyword co-occurrence networks, cluster analyses, and timeline views, providing researchers with diverse analytical perspectives. RStudio was used in conjunction with the "Bibliometrix" package to generate thematic maps and thematic evolution analyses.

In the visualized knowledge networks generated by CiteSpace, various elements are depicted through a topological structure to delineate the evolutionary characteristics of the research field. Nodes, as the fundamental units of the network, represent multiple academic entities (such as keywords, countries, institutions, journals), with their size being proportional to research activity or citation frequency. The lines connecting the nodes represent co-occurrence relationships; for instance, a topological link is formed between two countries or institutions when they co-author a paper. A color-mapping mechanism integrates the time dimension into the visualization: cool colors (like blue) represent data from earlier years, while warm colors (like red) indicate recent research output, thus forming a visual gradient of temporal evolution. Notably, a purple ring around a node highlights the strength of its Betweenness Centrality, an indicator that measures the pivotal role of a node in knowledge dissemination pathways. Nodes with high centrality often correspond to groundbreaking publications that connect different disciplines or to "knowledge gatekeepers" in social networks, exerting significant regulatory influence on the flow of knowledge within the field.[23] For further details, please refer to the relevant in-depth literature.[24]

The main operational steps in CiteSpace are as follows: First, a new CiteSpace project was created, and the full records obtained from the aforementioned search process were imported. Next, relevant parameters were configured within the project, including setting the Time Slicing to one-year intervals, analyzing the results year by year before merging them, and selecting authors, keywords, journals, categories, and references as node types for analysis. Detailed parameter configurations are provided in Supplementary Table 1. The specific parameters used in each analysis are indicated in the top-left corner of the corresponding figure.

In the cluster analysis of references and keywords, the Log-Likelihood Ratio (LLR) algorithm was used for term extraction to ensure the accuracy and reliability of the clustering. The top-left corner of the generated maps displays the Modularity Q value and the mean Silhouette S value, which are key indicators for evaluating the quality of the clustering. The range of the Q value is [0,1]; a $Q > 0.3$ indicates a significant cluster structure, $Q > 0.5$ suggests a reasonable clustering, and $Q > 0.7$ reflects a highly credible clustering result. For the burst detection of keywords and references, the γ value was set to 1.0 with a minimum duration of 1 year. Based on the co-occurrence relationships in citations, keyword co-occurrence maps, cluster maps, timeline views, and burst detection graphs were generated to comprehensively reveal the frequency, centrality, cluster structure, time span, and thematic evolution of keywords. The timeline view transforms the co-occurrence network into a chronological format with annual legend labels, allowing researchers to intuitively observe the evolution of research trends over time.[25]

Results

Annual Publication Trends and Overall Distribution

After rigorous screening, this study ultimately included 559 relevant documents (comprising 326 original research articles and 233 review articles) for bibliometric analysis (Figure 1). An analysis of annual publication trends (Figure 2A and B) revealed that the research output in this field can be divided into two phases: a period of steady development from 2009 to 2019, with an average of fewer than 30 publications per year, followed by a period of rapid growth from 2020 to 2023, with a surge in the number of documents. Notably, the cumulative number of publications in the last five years (2020–2024) reached 301, accounting for 53.8% of the total literature, and the annual publication count has exceeded 50 for four consecutive years since 2021. This clearly reflects that OV have become a prominent research hotspot in the field of glioma treatment. To further explore the macro-level layout of the research, a multi-dimensional network topological analysis (Figure 2C) revealed the intrinsic connections among countries, themes, and institutions. The analysis showed that the United States and China dominate the collaboration network in this field, with their core research institutions primarily focusing on therapeutic exploration for GBM using viral vectors represented by herpes-simplex-virus.

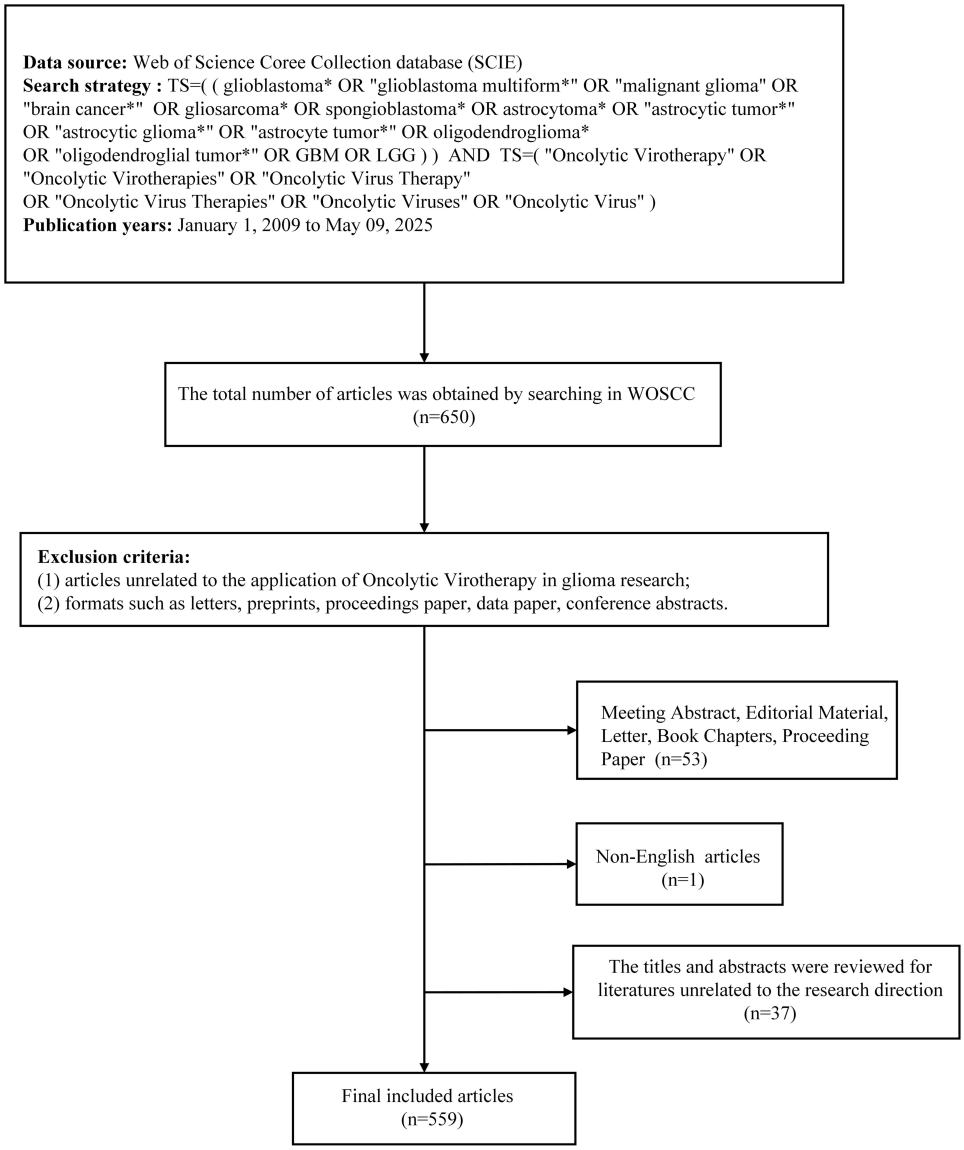

Figure 1 Flowchart of study identification and selection based on Web of Science Core Collection. The search strategy utilized Boolean operators (OR, AND) and truncation symbols. The asterisk (*) serves as a wildcard to retrieve variations of a root word (eg, "glioblastoma*" retrieves "glioblastoma" and "glioblastomas").
Abbreviations: SCIE, Science Citation Index Expanded; WOSCC, Web of Science Core Collection.

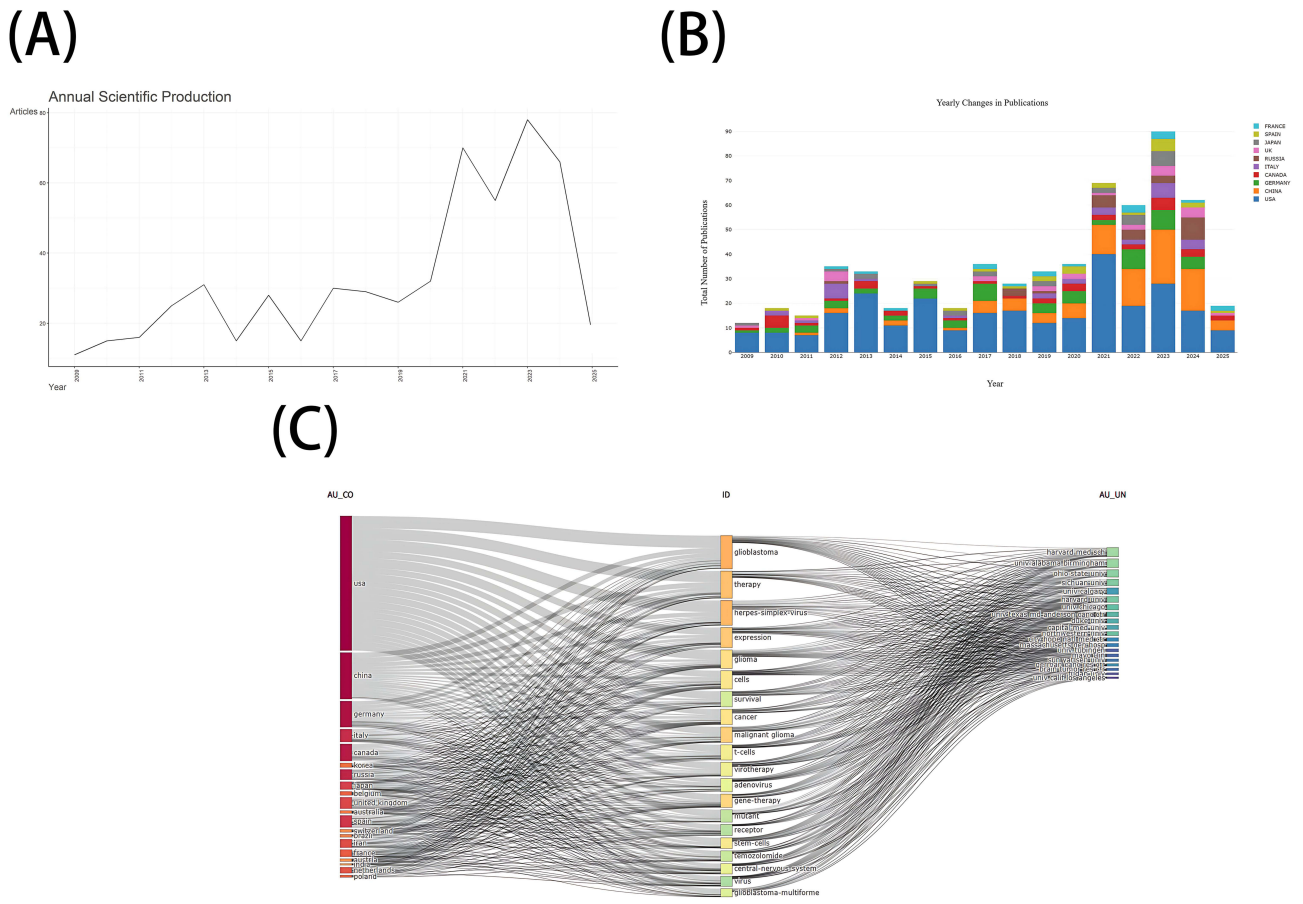

Figure 2 (**A**) Annual Scientific Production. (**B**) The annual number of publications in major countries. (**C**) RStudio - Three-fields plot left-countries, middle-keywords plus from the data records, right-authors affiliations.

Author and Co-Cited Author Analysis

The author collaboration network analysis showed that 495 authors constructed an academic network containing 894 collaboration links (Figure 3A). The ranking of prolific authors is shown in Table 1, with Chiocca, E Antonio leading with 23 publications, followed closely by Kaur, Balveen, Rabkin, Samuel D, Lesniak, Maciej S, and Wakimoto, Hiroaki. Co-citation analysis was used to reveal the knowledge base and core scholars of the field. The results indicated that Roger Stupp from the United States was the most frequently cited scholar, with E. Antonio Chiocca and James M. Markert also demonstrating significant academic influence (Table 2). In the co-cited author map (Figure 3B), the size of the nodes intuitively reflects the academic authority of the authors in this field.

Country and Institutional Collaboration Network Analysis

The country-level collaboration network consisted of 60 nodes and 164 links, covering all 559 publications (Figure 3C). As shown in Table 3, the United States and China hold an absolute advantage in terms of publication volume, with 227 (40.6%) and 95 (17.0%) publications, respectively, leading significantly. In terms of centrality, which reflects the influence within the collaboration network, the United States ranked first with a value of 0.67, underscoring its academic leadership. In contrast, although China had a high output, its centrality was only fifth (0.14), indicating that there is still room for improvement in the breadth and depth of its international collaborations. A noteworthy phenomenon is that Iran, despite having a modest number of publications, ranked fourth in centrality (0.17), suggesting its research may play a key bridging role in specific directions. The diagram of collaborative relationships between countries (Figure 3D) further shows that Germany, Canada, and France play important roles in promoting international academic exchange, while the research of some countries is relatively independent, necessitating stronger international cooperation in the future.

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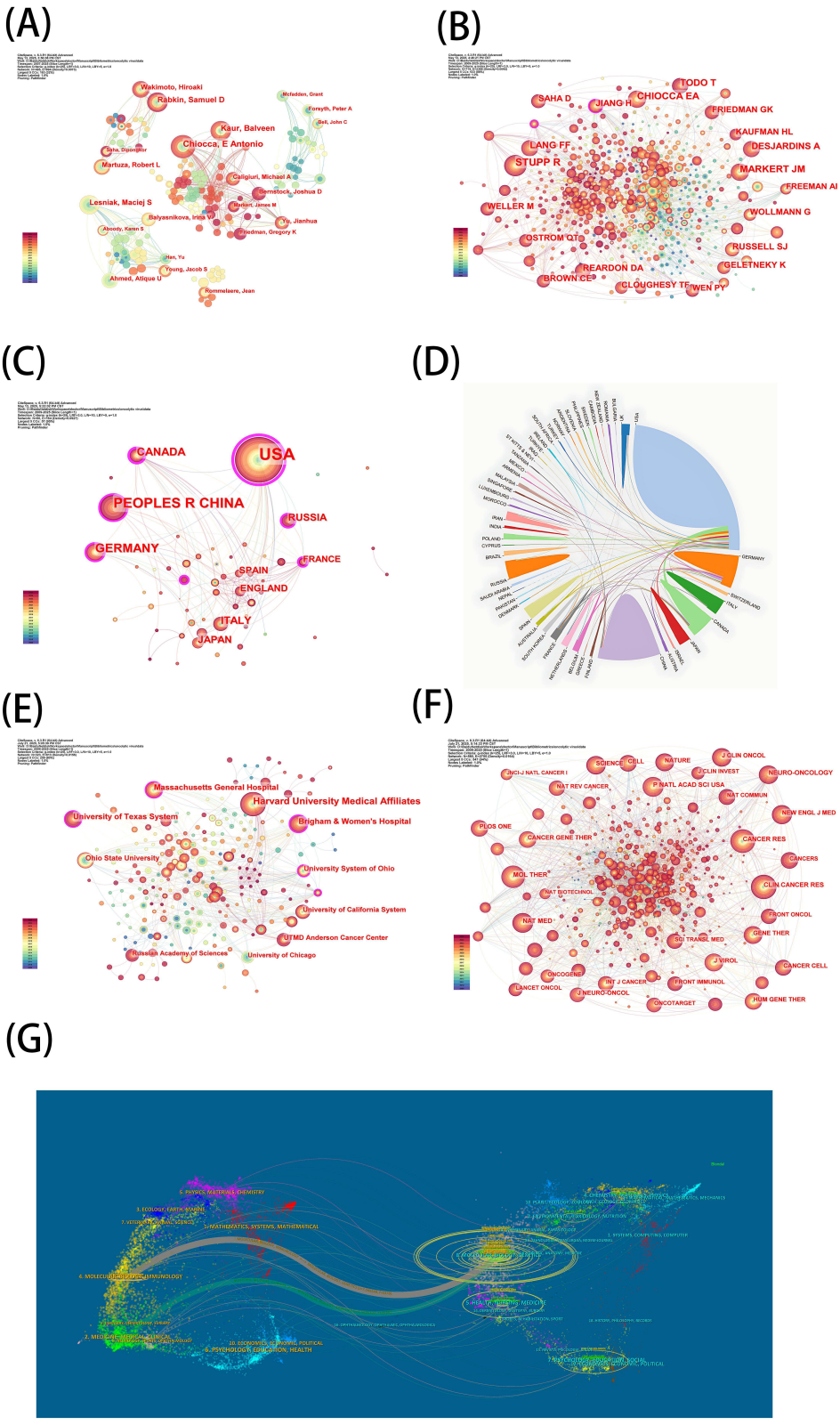

Figure 3 (**A**) Map of author related to oncolytic viruses in gliomas. (**B**) Map of cited author. (**C**) Map of countries. (**D**) Co-operation between countries/regions. (**E**) Map of institutions. (**F**) Cited journal maps. (**G**) The dual-map overlay of journals.

Table 1 The Top 5 Authors with the Most Publications

Rank	Author	Country	Institution	Publication
1	Chiocca, E Antonio	USA	Brigham and Women's Hospital	23
2	Kaur, Balveen	USA	Georgia Cancer Center at Augusta University	17
3	Rabkin, Samuel D	USA	Massachusetts General Hospital and Harvard Medical School	16
4	Lesniak, Maciej S	USA	Feinberg School of Medicine, Northwestern University	14
5	Wakimoto, Hiroaki	USA	Massachusetts General Hospital and Harvard Medical School	11

Table 2 The Top 5 Authors with the Most Citation Accounts

Rank	Author	Country	Institution	Frequency
1	Stupp, Roger	USA	Northwestern University	228
2	Chiocca, E Antonio	USA	Brigham and Women's Hospital	165
3	Markert, James M	USA	University of Alabama at Birmingham	161
4	Lang, Frederick F	USA	The University of Texas MD Anderson Cancer Center	138
5	Desjardins, Annick	USA	Duke University	133

Table 3 The Top 5 Countries with the Most Publications and Centrality

Rank	Publications	Countries	Rank	Centrality	Countries
1	277	USA	1	0.67	USA
2	95	Peoples R China	2	0.19	Germany
3	59	Germany	3	0.19	Canada
4	36	Canada	4	0.17	Iran
5	30	Italy	5	0.14	Peoples R China

The institutional collaboration network included 323 institutional nodes and 813 collaboration links (Figure 3E). The top five institutions in terms of output and centrality are listed in Table 4. Among them, Harvard University Medical Affiliates (77 publications) and Brigham & Women's Hospital (38 publications) ranked highest in publication volume. In terms of centrality, Brigham & Women's Hospital (0.21) was first, followed by the Institut National de la Sante et de la Recherche Medicale (0.18) and Massachusetts General Hospital (0.13). These data indicate that the aforementioned institutions are not only core production units in the field but also play pivotal roles in the international collaboration network.

Journal and Citation Network Analysis

An analysis of core journals showed that the top 10 journals by publication volume collectively published 171 articles, accounting for 30.6% of the total, with an average impact factor of 6.1 (Table 5). The journal citation network consisted of 580 nodes and 2755 links, forming a complex knowledge exchange network (Figure 3F). Among them, Cancer Research was the most frequently cited journal (449 times), followed by Clinical Cancer Research (440 times) and Molecular Therapy (433 times) (Table 6). The dual-map overlay of journals (Figure 3G) intuitively reveals the

Table 4 The Top 5 Institutions with the Most Publications and Centrality

Rank	Publications	Institutions	Rank	Centrality	Institutions
1	77	Harvard University Medical Affiliates	1	0.21	Brigham & Women's Hospital
2	38	Brigham & Women's Hospital	2	0.18	Institut National de la Sante et de la Recherche Medicale
3	37	Massachusetts General Hospital	3	0.13	Massachusetts General Hospital
4	34	University of Texas System	4	0.11	University System of Ohio
5	26	University System of Ohio	5	0.1	University of Texas System

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Table 5 The Top 10 Journals with the Most Publications

Rank	Publications	Journal	IF (Quartile in Category)
1	37	*Cancers*	4.4 (Q1)
2	24	*International Journal of Molecular Sciences*	4.9 (Q2)
3	21	*Viruses*	3.5 (Q1)
4	20	*Frontiers in Immunology*	5.9 (Q1)
5	15	*Neuro-Oncology*	13.4 (Q1)
6	14	*Cancer Gene Therapy*	5.0 (Q1)
7	13	*Journal of Virology*	3.8 (Q1)
8	10	*Molecular Therapy*	12.0 (Q1)
9	9	*Frontiers in Oncology*	3.3 (Q2)
10	8	*Gene Therapy*	4.5 (Q1)

Table 6 The Top 10 Cited Journals with the Most Citation Counts and Centrality

Rank	Cited Journal	Frequency	Rank	Cited Journal	Centrality
1	Cancer Res	449	1	*Cytokine Growth F R*	0.07
2	*Clin Cancer Res*	440	2	*Oncol Rep*	0.07
3	*Mol Ther*	433	3	*J Neuroimmunol*	0.07
4	*P Natl Acad Sci Usa*	408	4	*Nat Biotechnol*	0.05
5	*Neuro-Oncology*	379	5	*Brit J Cancer*	0.05
6	*Nat Med*	348	6	*Curr Cancer Drug Tar*	0.05
7	*New Engl J Med*	339	7	*Cell Death Differ*	0.05
8	*J Clin Oncol*	319	8	*Cancer Lett*	0.04
9	*Science*	311	9	*Acta Neuropathol*	0.04
10	*Nature*	310	10	*Anticancer Res*	0.04

knowledge flow path in the field: citing literature is mainly concentrated in clinical application areas such as "Immunology" and "Clinical Medicine/Neurology", while cited literature primarily originates from basic science fields like "Molecular/Biology/Genetics." This clear knowledge translation path from basic science to clinical application can provide an important reference for researchers in the field for journal selection and literature tracing.

Reference and Knowledge Base Analysis

The reference co-citation network, composed of 857 nodes and 2237 links, delineates the knowledge base of the field (Figure 4A). The most frequently cited publications primarily focus on clinical trials of key viral vectors (DNX-2401, recombinant poliovirus) and the efficacy of immune checkpoint inhibitors (nivolumab) in recurrent GBM[1,10,15,26–32] (Table 7). To identify rapidly developing research frontiers, this study conducted a reference burst detection analysis. The results (Figure 4B) show that the majority of burst literature is concentrated between 2018 and 2023, with five high-intensity bursts occurring since 2023, indicating that clinical application research on OV is in an accelerated development phase.[1,8,10,14,15,26–30,32–46] The timeline view of the clusters (Figure 4C) further reveals the evolution of research themes. While early hotspots such as oncolytic h-1 parvovirus and newcastle disease virus still receive attention, the focus on emerging themes like immunotherapy is rapidly increasing, becoming a current research hotspot.

Keyword Evolution and Research Hotspot Analysis

The keyword co-occurrence network contained 433 nodes and 1897 links (Figure 4D), with high-frequency and high-centrality keywords listed in Table 8. In addition to oncolytic virus and gene therapy, GBM, stem cells, HSV, and Phase I trial are core research topics in the field. Keyword cluster analysis categorized these topics into 11 main research directions (Figure 4E), including #0 immunotherapy, #1 alpha dystroglycan, #2 combination, and #3 newcastle disease virus.

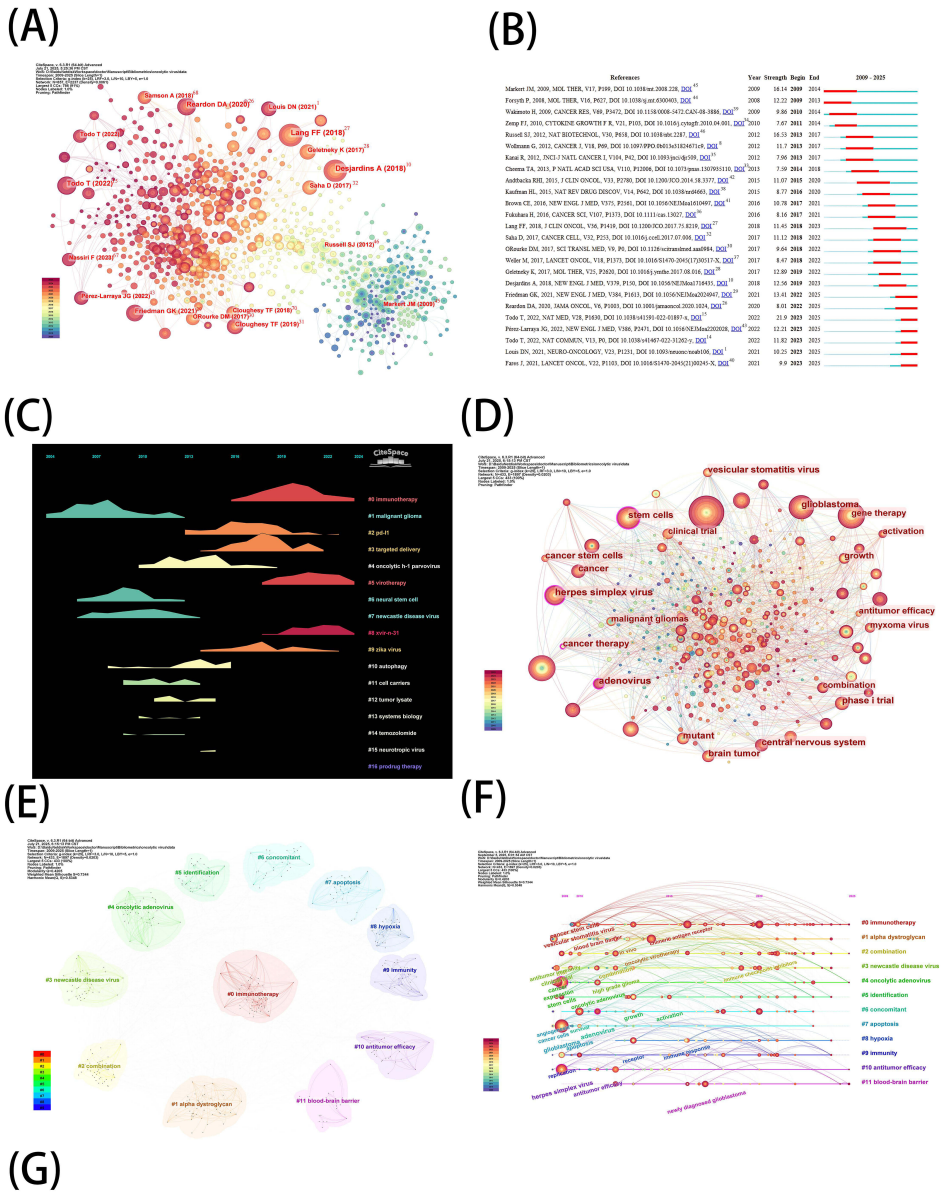

Figure 4 (**A**) Map of cited references. (**B**) The top 25 references with the strongest citation bursts. The blue bars indicate that the reference has been published; the red bars indicate citation burstness. (**C**) The visualization map of the timeline viewer. (**D**) Map of keywords occurrence. (**E**) The clustering of keywords. (**F**) Time dynamic evolution of keywords. (**G**) The top 15 keywords with the strongest citation bursts. The blue bars indicate that the reference has been published; the red bars indicate citation burstness.

Table 7 The Top 10 Cited References with the Most Citation Counts References

Rank	Frequency	Article Title	Authors & Year	Main Findings
1	89	Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma[27]	Lang, Frederick F, et al, 2018	DNX-2401 results in long-term survival in recurrent high-grade glioma through direct oncolysis followed by an immune response.
2	88	Recurrent glioblastoma treated with recombinant poliovirus[10]	Desjardins A et al, 2018	Intratumoral infusion of recombinant poliovirus (PVSRIPO) resulted in a durable survival benefit in patients with recurrent glioblastoma.
3	61	Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial[26]	Reardon DA et al, 2020	Nivolumab did not improve overall survival compared with bevacizumab in patients with recurrent glioblastoma in this trial.
4	57	Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a phase 2 trial[15]	Todo T et al, 2022	Repeated intratumoral G47Δ demonstrates a significant survival benefit and good safety profile in recurrent glioblastoma patients.
5	46	Oncolytic HSV-1 G207 immunovirotherapy for pediatric high-grade gliomas[29]	Friedman GK et al, 2021	Intratumoral G207 is safe for pediatric high-grade glioma, showing responses and converting immunologically "cold" tumors to "hot".
6	44	Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma[31]	Cloughesy TF et al, 2019	Neoadjuvant anti-PD-1 immunotherapy significantly extended overall survival in recurrent glioblastoma compared to adjuvant-only therapy.
7	39	Oncolytic H-1 parvovirus shows safety and signs of immunogenic activity in a first phase I/IIa glioblastoma trial[28]	Geletneky K et al, 2017	H-1 parvovirus (H-1PV) is safe for glioblastoma patients, crosses the blood-brain barrier, and triggers immunogenic activity.
8	38	Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade[32]	Saha D et al, 2017	Triple combination of oHSV expressing IL-12 and dual checkpoint inhibitors cured mouse glioblastoma, requiring T cells and macrophages.
9	36	The 2021 WHO Classification of Tumors of the Central Nervous System: a summary[1]	Louis DN et al, 2021	The 2021 WHO classification for CNS tumors integrates molecular diagnostics, leading to new tumor types and revised nomenclature
10	33	A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma[30]	ORourke DM et al, 2017	Peripherally infused EGFRvIII-directed CAR T-cells traffic to GBM, mediate antigen loss, and induce an adaptive resistant tumor microenvironment

The temporal analysis of keywords (Figure 4F and G) clearly illustrates the dynamic evolution of research hotspots. Before 2020, research hotspots primarily revolved around basic and early clinical explorations such as HSV, apoptosis, and dendritic cell vaccination. Since 2020, the research focus has significantly shifted towards immunotherapy, combination, and tumor microenvironment, with the continuous emergence of keywords like recurrent GBM and dose escalation, marking the entry of research into a deeper phase of clinical application and mechanistic exploration.

Disciplinary Thematic Structure and Evolutionary Path

To grasp the thematic structure of the discipline at a macro level, this study constructed a strategic diagram (Figure 5A). This diagram, with centrality (representing the pivotal nature of a theme) and density (representing the maturity of a theme) as its axes, divides research themes into four quadrants. The results show that the field has formed a mature disciplinary structure dominated by "core-driving themes" in the first quadrant, with a balanced distribution of themes across all quadrants. "Core-driving themes" represent mainstream research directions, "specialized-niche themes" (second quadrant) have independent research systems, and "emerging/declining themes" (third quadrant) and "foundational themes" (fourth quadrant) represent future development potential and the discipline's foundation, respectively.

Table 8 The Top 10 Keywords with the Most Citation Count and Centrality

Rank	Frequency	Keyword	Rank	Centrality	Keyword
1	247	Oncolytic virus	1	0.04	Oncolytic virus
2	164	Gene therapy	2	0.11	Adenovirus
3	147	Glioblastoma	3	0.1	Stem cells
4	143	Malignant glioma	4	0.1	Herpes simplex virus
5	105	Stem cells	5	0.1	Growth
6	103	Herpes simplex virus	6	0.1	Cancer therapy
7	66	Expression	7	0.09	Glioblastoma
8	63	Oncolytic virotherapy	8	0.09	Cancer
9	62	Cancer	9	0.09	Phase i trial
10	57	Phase i trial	10	0.09	Activation

Thematic evolution analysis based on a time series (Figure 5B) further deconstructs the research progress into four stages: the technological exploration period (2009–2013), the clinical validation period (2014–2017), the disciplinary integration period (2018–2021), and the emerging development stage (2022–2025). The research trajectory shows that oncolytic virus therapy has undergone a paradigm shift from early basic exploration of the feasibility of specific viruses (like herpes-simplex-virus) in malignant glioma, to a clinical validation paradigm combining immunotherapy for GBM, and finally deepening into the current in-depth integrated research on host immune responses (like t-cells) and tumor cell molecular mechanisms (like dna-damage response, metabolism).

Discussion

This study, through bibliometric methods, has systematically and comprehensively analyzed the research dynamics, knowledge structure, and developmental trends in the field of oncolytic virus therapy for glioma over the past 16 years. The results clearly indicate that the field is undergoing unprecedented rapid development, and its research paradigm has undergone a profound transformation. Our analysis not only quantifies the global research output and collaboration landscape but also reveals a clear evolutionary path from basic virology exploration to complex immune combination therapy strategies, providing a macro-level perspective for understanding the current state and predicting future directions of the field.

Overall Trends and Key Turning Points: A Burgeoning Research Field

Our analysis reveals that research on oncolytic virus therapy for glioma entered an "explosive" growth period after 2020, with the publication volume in the last five years accounting for more than half of the total literature. This trend is not coincidental but is driven by a series of major scientific breakthroughs and clinical advancements. A key milestone event was the approval of the genetically engineered HSV G47Δ (Teserpaturev/DELYTACT®) by the Japanese Ministry of Health, Labour and Welfare in 2021 for the treatment of malignant glioma, making it the world's first oncolytic virus product approved for brain tumor therapy. This approval was based on a successful Phase II clinical trial that achieved a one-year survival rate of up to 84.2% in patients with recurrent GBM, far exceeding historical controls.[15] This approval greatly boosted the confidence of researchers worldwide, validated the clinical feasibility of oncolytic virus therapy, and directly spurred the initiation of numerous subsequent studies and clinical trials, which perfectly aligns with our observation of annual publication counts consistently exceeding 50 since 2021. Furthermore, as early as 2015, the oncolytic virus T-VEC was approved by the US FDA for the treatment of melanoma. Although its indication was not glioma, as the first approved oncolytic virus drug, it laid the foundation for the development of the entire oncolytic virus field and stimulated its application in other "cold tumors", including glioma.[42] Another bibliometric analysis on the combination of OV and immunotherapy also identified 2014 as a watershed year for the development of this intersecting field,[47] marking a sharp increase in research interest. This corresponds with the starting point of growth observed in our study, jointly confirming that oncolytic virus therapy, especially in combination with immunotherapy, is one of the most dynamic frontiers in oncology in recent years.

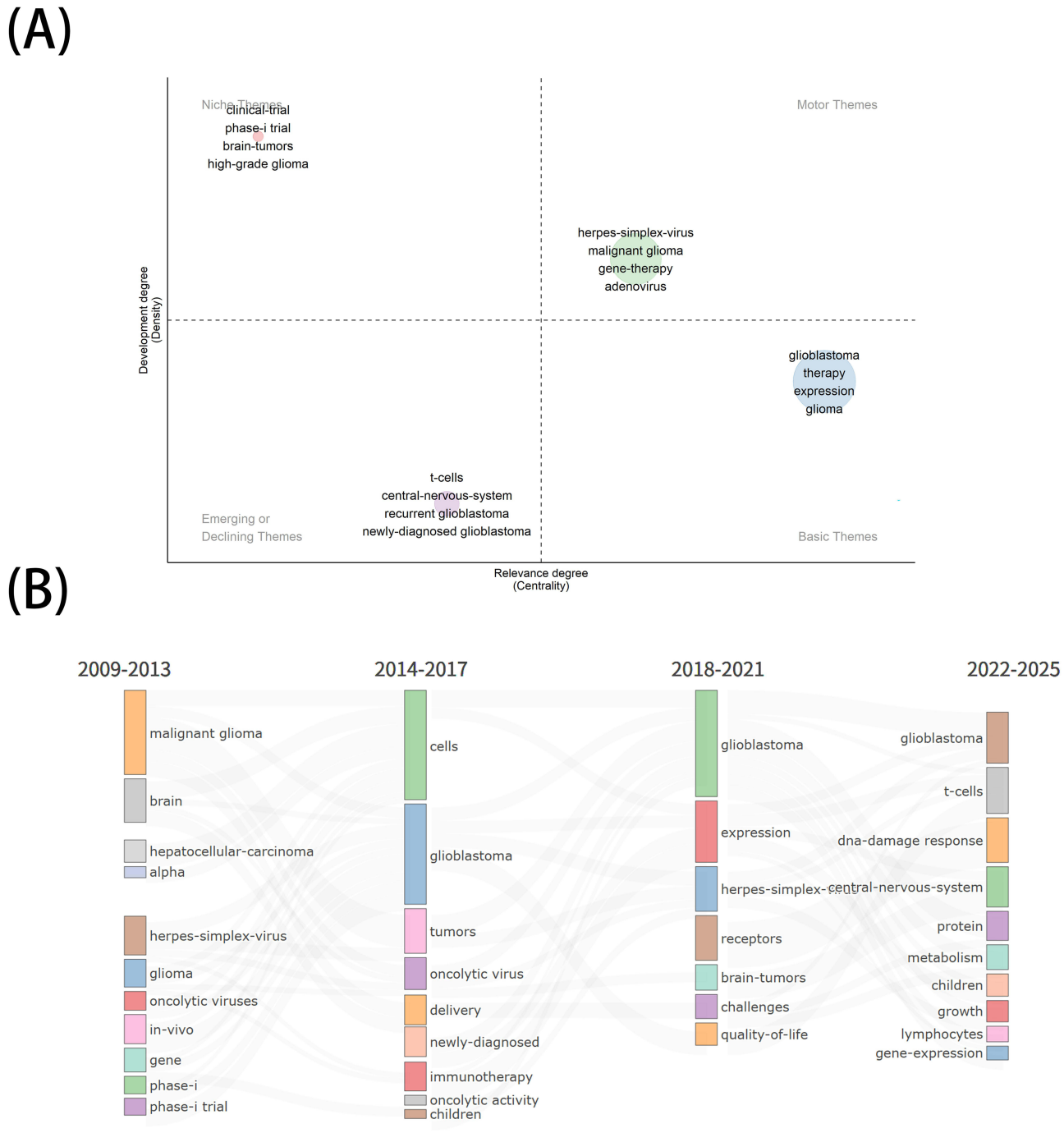

Figure 5 (**A**) The strategy map of identified topics clustered by keywords plus. (**B**) Thematic Evolution of oncolytic viruses in gliomas research from 2009 to 2025.

Global Research Landscape: Leaders and Followers in the Collaboration Network

From the perspective of country and institutional contributions, the United States is undoubtedly the global leader in this field. It not only holds an absolute advantage in the number of publications but also leads significantly in the centrality of its collaboration network. This is backed by its strong research foundation and continuous financial investment. As pointed out by Cheng et al, institutions like the United States National Institutes of Health and the National Cancer Institute have provided the vast majority of research funding for this field, ensuring support for high-quality, large-scale research.[19] Concurrently, the core high-producing institutions identified in this study, such as Harvard University and Brigham and

Women's Hospital, are all located in the United States. These institutions are not only powerhouses of basic research but also the initiators and executors of many key clinical trials, forming a complete research chain from bench to bedside.

At the author level, the research directions of the highly productive scholars identified in this study constitute the core pillars of the field's development. The top-ranking prolific author, Professor Chiocca, E Antonio, is a key figure in advancing OV from the laboratory to the clinic, having led several important Phase I clinical trials covering different viral platforms and therapeutic strategies. For instance, he led the first-in-human trial of rQNestin34.5v.2 (CAN-3110), a novel oncolytic virus where the HSV neurovirulence gene is placed under the control of the tumor-specific nestin promoter.[48] Additionally, he has been deeply involved in cutting-edge clinical research on regulatable IL-12 gene therapy (Ad-RTS-hIL-12) combined with the PD-1 inhibitor nivolumab, as well as cytotoxic immunotherapy mediated by the adenoviral vector AdV-tk.[49–51] Professor Rabkin, Samuel D, is a pioneer in viral genetic engineering and the exploration of immune mechanisms. He was one of the core developers of the G47Δ virus and has revealed the synergistic mechanisms of combining OV with immune checkpoint inhibitors for glioma treatment through in-depth research. His discovery that macrophage polarization plays a key role in combined immuno-virotherapy provides a crucial theoretical basis for optimizing combination regimens.[32,52,53] Professor Kaur, Balveen's research focuses on the interaction between the tumor microenvironment and OV. She pioneered the exploration of the synergistic effects of oncolytic HSV with epigenetic drugs like histone deacetylase (HDAC) inhibitors, demonstrating that modulating the tumor microenvironment can significantly enhance the virus's anti-tumor activity, thus opening new avenues for combination therapy.[54,55] Professor Lesniak, Maciej S, is dedicated to solving the core challenge of oncolytic virus delivery. He innovatively used stem cells as "Trojan horse" vectors. Notably, he led the first-in-human Phase I clinical trial using neural stem cells to deliver an oncolytic adenovirus, successfully validating the safety and feasibility of this strategy and providing an innovative solution for overcoming the blood-brain barrier.[40,56,57] The work of these top scholars, along with the foundational contributions of the highly cited scholar Stupp, Roger, in standard chemotherapy for glioma,[2] collectively paints a comprehensive picture of the field, from viral design, mechanistic exploration, microenvironment modulation, and innovative delivery to clinical validation.

Compared to the United States, China, although performing impressively in publication volume, ranking second, has a lower centrality in the collaboration network. This suggests that while China's research output is high, it may be more concentrated on domestic collaborations, and its leadership role and influence in the global academic network have yet to be fully realized. This phenomenon is similar to findings in bibliometric analyses of other fields, suggesting that strengthening international, especially East-West, substantive collaboration is crucial for promoting the synergistic development of the entire field.

Evolution of the Research Paradigm: A Profound Shift from Viral Oncolysis to Immune Synergy

One of the most central findings of this study is the clear delineation of a profound shift in the research paradigm of the field, as revealed through keyword evolution and thematic change analysis. This shift can be summarized as an evolution from early "virus-centric oncolytic exploration" to the current "immunity-centric synergistic therapy."

During the technological exploration period (2009–2013), core keywords were focused on HSV, adenovirus, gene therapy, and phase-i trial. This reflects that the primary task of early research was to develop and validate the viral vectors themselves. Researchers were dedicated to improving viral safety and tumor-targeting specificity through genetic engineering techniques, such as deleting viral neurovirulence genes (eg, the γ134.5 gene of HSV-1) or inserting tumor-specific promoters, and conducting preliminary Phase I clinical trials to verify their safety in humans.[45,49,53,58] The focus at this stage was on whether the virus could safely and effectively replicate within tumor cells and directly cause their lysis. Currently, various viral platforms have been developed for glioma treatment, including HSV-1, adenovirus, poliovirus, and reovirus, and have shown encouraging prospects in preclinical and early clinical trials, as summarized in Supplementary Table 2.

As research deepened, especially during the clinical validation period (2014–2017) and the disciplinary integration period (2018–2021), the emergence and rapid rise of immunotherapy as a core theme marked the first major leap in the

research paradigm. Researchers gradually realized that the true power of OV lies not only in their direct cell-killing effect but also in their potent ability to reshape the Tumor Microenvironment (TME).[59] Glioma, particularly GBM, is a classic immunologically "cold" tumor, characterized by an immunosuppressive TME and a lack of T-cell infiltration.[60] By inducing Immunogenic Cell Death (ICD), OV release a large number of tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns (PAMPs), effectively transforming "cold" tumors into immunologically "hot" ones. This attracts and activates immune cells, thereby initiating a powerful and durable anti-tumor immune response.[38,61,62] The dual-map overlay analysis of journals also corroborates this point, showing a knowledge flow where basic research from the "Molecular/Biology/Genetics" field is ultimately widely cited by journals in the "Immunology" and "Clinical Medicine" fields, perfectly illustrating the knowledge translation path from basic virology and genetics to clinical immunotherapy.

Entering the emerging development stage (2022–2025), the burst of keywords such as combination, t-cells, tumor microenvironment, dna-damage response, and metabolism signifies that the research paradigm is evolving towards a deeper and more refined direction. This indicates that current research is no longer satisfied with simple combinations of viruses and immune checkpoint inhibitors but is beginning to deeply explore the intrinsic mechanisms of combination therapy, focusing on the central role of T cells, and how viruses affect tumor cell DNA damage repair and metabolic pathways to identify new synergistic targets.[63]

Current Research Hotspots and Future Frontiers: Combination, Precision, and Personalization

Our analysis has identified several major research hotspots in the field today, which not only are high-frequency themes in the literature but also represent the most promising future directions.

First, combination immunotherapy is the absolute core at present. Glioma has an extremely low response rate to single immunotherapies, including ICIs, primarily due to the strong immunosuppression of its TME and low tumor mutational burden.[64] The "heating" effect of OV precisely compensates for the shortcomings of ICIs. A large body of preclinical and clinical research has confirmed that OV can upregulate the expression of PD-L1 on tumor cells and increase the infiltration of cytotoxic T lymphocytes (CTLs), thereby creating a favorable environment for ICIs (such as anti-PD-1/PD-L1 antibodies) to work. Their combination can produce a synergistic effect of "1+1>2".[65–68] For example, the breakthrough success of the PVSRIPO virus Phase I clinical trial was due to its induction of a durable immune response in patients with recurrent GBM, resulting in 21% of patients remaining alive at 24 and 36 months, an unprecedented outcome in recurrent GBM, which lacks effective treatment options.[10] Besides ICIs, the combination of OV with other therapies is also being actively explored. An emerging and highly promising direction is the combination of OV and Tumor Treating Fields (TTFields). TTFields inhibit tumor cell proliferation by interfering with mitosis, while OV induce ICD. Their mechanisms are complementary and expected to produce a synergistic killing effect, providing new ideas for future clinical trial designs.[69]

Second, innovation in virus delivery systems is a critical bottleneck that urgently needs to be overcome. Our keyword analysis shows that the word "delivery" has exhibited a strong burst in recent times. The blood-brain barrier (BBB) is the main obstacle to the systemic delivery of drugs for brain tumor treatment. Therefore, the vast majority of current clinical trials use intratumoral injection for drug administration, but this faces limitations of uneven virus distribution and the inability to cover infiltrative tumor cells.[40,70] To overcome these challenges, various innovative delivery strategies are being explored. For instance, Convection-Enhanced Delivery (CED) technology can distribute the virus more widely throughout the brain parenchyma by establishing a pressure gradient within or around the tumor; the PVSRIPO clinical trial successfully applied this technique.[10] Furthermore, using stem cells with natural tropism as viral vectors, such as neural stem cells (NSCs), is another highly promising direction.[40] The latest research progress also points to more advanced technologies, such as using Focused Ultrasound (FUS) to transiently and non-invasively open the local BBB, creating a "window of opportunity" for intravenously injected OV to enter the brain tumor.[71] Concurrently, using aptamers to modify the surface of OV, enabling them to specifically recognize markers on the surface of glioma cells (such as EGFRvIII or Tenascin-C),

and thus achieve precise targeting like "biological missiles" to minimize damage to normal brain tissue, is also an important future direction for delivery technology.[72]

Third, personalized and precision virotherapy is the inevitable trend for the future. Glioma exhibits high intra- and inter-tumoral heterogeneity, meaning a "one-size-fits-all" treatment approach is unlikely to succeed. However, there is still a lack of effective biomarkers to predict which patients will benefit from specific oncolytic virus therapies. A systematic review pointed out that common molecular subtypes, such as IDH mutation or MGMT promoter methylation status, do not effectively predict the efficacy of OV, a view our results indirectly support.[73] Therefore, a key future research focus is to find reliable predictive biomarkers for efficacy, such as the status of the interferon pathway in tumor cells or the expression level of specific viral receptors. At the same time, tailoring treatment plans for specific patient populations is already showing initial success. For example, in a Phase I clinical trial for pediatric high-grade glioma, the G207 virus combined with a single low dose of radiation (5 Gy) was proven to be safe and effective, providing valuable clinical evidence for treating this challenging patient group.[29] Furthermore, patient-derived organoids (PDOs) and other 3D culture models offer a powerful platform for the preclinical screening of the most suitable oncolytic virus for an individual patient.[74] By testing a range of different OV on these models, which highly mimic the in vivo tumor microenvironment, individualized "virograms" can be constructed, thereby achieving true personalized precision medicine.[75]

Limitations

Although this study employed multiple bibliometric tools, combining co-word analysis and literature review to systematically analyze the research landscape of OV in glioma treatment, some inherent limitations need to be acknowledged. First, the literature search for this study has a cutoff date of May 9, 2025, but the WOSCC database is continuously updated, and a large number of new publications from 2025 are still being indexed, which may have led to us not fully capturing the latest research dynamics. Second, this study only searched the WOSCC database, which might have missed some relevant literature indexed only in other important databases such as PubMed, Scopus, and Embase. Future research could consider expanding the data sources to increase data diversity and comprehensiveness. Third, this study was limited to English-language literature, which may overlook important research findings published in other languages, thereby restricting a comprehensive understanding of the research landscape in this field on a global scale. Finally, although bibliometric tools like CiteSpace are powerful in processing large-scale datasets, mapping knowledge, and identifying trends, they also have methodological limitations. For example, the algorithms used for clustering and label extraction (such as the log-likelihood ratio algorithm) may not fully capture the nuances of a research area, and their results are influenced by parameter settings and the quality of the input data. Automatically generated cluster labels might be too broad (eg, "#0 immunotherapy") or too specific (eg, "#1 alpha dystroglycan"), requiring careful interpretation by researchers with domain expertise. More importantly, the core of bibliometric analysis is publication metrics (such as publication count, citation frequency), which cannot directly assess the clinical quality, validity, or strength of evidence of a single study. Furthermore, bibliometric analysis has inherent limitations in relation to clinical translation, as it primarily relies on published literature and citation metrics, which may not fully capture ongoing clinical trials, unpublished data (eg, negative results), real-world implementation barriers, or the practical challenges of translating research findings into patient care. Therefore, the findings of this study reflect the structure and hotspots of published academic literature, rather than a clinical practice consensus or proven therapeutic efficacy. Future work could combine such macro-level bibliometric analysis with in-depth systematic qualitative reviews to provide a more multi-faceted and comprehensive assessment of the field. Despite these limitations, we believe this study still provides a valuable, objective, and macro-level reference for understanding the knowledge base, evolutionary path, and future frontiers of oncolytic virus therapy for glioma.

Conclusion

In summary, the field of oncolytic virus therapy for glioma has made significant progress over the past 16 years and is advancing at an unprecedented pace. The research paradigm has successfully shifted from focusing on the oncolytic effect of the virus itself to a new era of combination therapy centered on its immune-activating capabilities. Current research hotspots are highly concentrated on the synergistic potentiation of OV with immunotherapies like immune checkpoint inhibitors and CAR-T, as well as with therapies like TTFields. Meanwhile, overcoming the blood-brain barrier through innovative technologies

such as focused ultrasound, stem cell carriers, and aptamers to achieve efficient and precise viral delivery, and using biomarkers to guide personalized treatment, represent the core challenges and most promising breakthrough directions for the field.

The knowledge map and development roadmap generated by this study provide a clear, data-driven framework for researchers, clinicians, and policymakers. These bibliometric insights—specifically the identification of key research hotspots and emerging trends—can directly inform clinical translation by guiding the design of more effective clinical trials, prioritizing resources for promising areas like personalized virotherapy, and fostering strategic collaborations between leading institutions. Ultimately, this comprehensive understanding can help accelerate the development of evidence-based protocols and translate this promising therapy into tangible survival benefits for patients with glioma.

Abbreviations

GBM, glioblastoma; OV, Oncolytic viruse; TEM, Transmission Electron Microscopy; COVID-19, Coronavirus Disease 2019; ICIs, immune checkpoint inhibitors; WOSCC, Web Of Science Core Collection; LLR, Log-Likelihood Ratio; IF, Impact Factor; HDAC, histone deacetylase; HSV, Herpes Simplex Virus; TME, Tumor Microenvironment; ICD, Immunogenic Cell Death; TAAs, tumor-associated antigens; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PD-L1, Programmed Death-Ligand 1; CTLs, cytotoxic T lymphocytes; PVSRIPO, Poliovirus Sabin-Rhinovirus IRES Poliovirus; TTFields, Tumor Treating Fields; BBB, blood-brain barrier; FUS, Focused Ultrasound; PDOs, patient-derived organoids.

Data Sharing Statement

The data used in this study are derived from the Web of Science Core Collection, a publicly accessible database. The bibliometric analysis conducted utilized data on publications from January 1, 2009, to May 9, 2025, focusing on research related to oncolytic virus therapy for gliomas. The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Any additional information or data supporting the findings of this study are also available from the corresponding author on request.

Ethics Approval and Consent to Participate

This study is a bibliometric analysis based exclusively on previously published literature retrieved from the Web of Science Core Collection database. All data used in this study are publicly available and were analyzed in an aggregated, anonymized format. Therefore, this research does not involve human subjects, human material, or human data in a manner that would require direct ethical approval or patient informed consent. In accordance with national legislation, specifically item 1 of Article 32 of the "Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects" issued on February 18, 2023, by the People's Republic of China, research utilizing legally obtained public data is exempt from ethical review. As our study strictly adheres to these conditions, formal ethical approval from an Institutional Review Board (IRB) was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. Louis DN, Perry A, Wesseling P. et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-Oncology*. 2021;23(8):1231–1251. doi:10.1093/neuonc/noab106
2. Stupp R, Mason WP, Van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996. doi:10.1056/nejmoa043330
3. Price M, Ballard C, Benedetti J, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2017–2021. *Neuro oncol*. 2024;26(Supplement_6):vi1–vi85. doi:10.1093/neuonc/noae145
4. Grochans S, Cybulska AM, Simińska D, et al. Epidemiology of glioblastoma multiforme–literature review. *Cancers*. 2022;14(10):2412. doi:10.3390/cancers14102412
5. Terrível M, Gromicho C, Matos AM. Oncolytic viruses: what to expect from their use in cancer treatment. *Microbiol Immunol*. 2020;64 (7):477–492. doi:10.1111/1348-0421.12753
6. Torge D, Bernardi S, Ciciarelli G, Macchiarelli G, Bianchi S. Dedicated protocol for ultrastructural analysis of farmed rainbow trout (oncorhynchus mykiss) tissues with red mark syndrome: the skin—part one. *Methods Protoc*. 2024;7(3):37. doi:10.3390/mps7030037
7. Raja J, Ludwig JM, Gettinger SN, Schalper KA, Kim HS. Oncolytic virus immunotherapy: future prospects for oncology. *J ImmunoTher Cancer*. 2018;6(1). doi:10.1186/s40425-018-0458-z
8. Wollmann G, Ozduman K, Van Den Pol AN. Oncolytic virus therapy for glioblastoma multiforme: concepts and candidates. *Cancer J*. 2012;18 (1):69–81. doi:10.1097/ppo.0b013e31824671c9
9. Ramachandran M, Yu D, Dyczynski M, et al. Safe and effective treatment of experimental neuroblastoma and glioblastoma using systemically delivered triple MicroRNA-detargeted oncolytic semliki forest virus. *Clin Cancer Res*. 2017;23(6):1519–1530. doi:10.1158/1078-0432.ccr-16-0925
10. Desjardins A, Gromeier M, Herndon JE, et al. Recurrent glioblastoma treated with recombinant poliovirus. *N Engl J Med*. 2018;379(2):150–161. doi:10.1056/nejmoa1716435
11. Torge D, Bernardi S, Arcangeli M, Bianchi S. Histopathological features of SARS-CoV-2 in extrapulmonary organ infection: a systematic review of literature. *Pathogens*. 2022;11(8):867. doi:10.3390/pathogens11080867
12. Thomas AA, Brennan CW, DeAngelis LM, Omuro AM. Emerging therapies for glioblastoma. *JAMA Neurol*. 2014;71(11):1437. doi:10.1001/jamaneurol.2014.1701
13. Mathios D, Kim JE, Mangraviti A, et al. Anti–PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM. *Sci Transl Med*. 2016;8(370). doi:10.1126/scitranslmed.aag2942
14. Todo T, Ino Y, Ohtsu H, Shibahara J, Tanaka M. A phase I/II study of triple-mutated oncolytic herpes virus G47Δ in patients with progressive glioblastoma. *Nat Commun*. 2022;13(1). doi:10.1038/s41467-022-31262-y
15. Todo T, Ito H, Ino Y, et al. Intratumoral oncolytic herpes virus G47Δ for residual or recurrent glioblastoma: a Phase 2 trial. *Nat Med*. 2022;28 (8):1630–1639. doi:10.1038/s41591-022-01897-x
16. Taguchi S, Fukuhara H, Todo T. Oncolytic virus therapy in Japan: progress in clinical trials and future perspectives. *Jpn J Clin Oncol*. 2019;49 (3):201–209. doi:10.1093/jjco/hyy170
17. Chen Y, Long T, Xu Q, Zhang C. Bibliometric analysis of ferroptosis in stroke from 2013 to 2021. *Front Pharmacol*. 2022;12. doi:10.3389/fphar.2021.817364
18. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. *J Bus Res*. 2021;133:285–296. doi:10.1016/j.jbusres.2021.04.070
19. Cheng K, Zhang H, Guo Q, et al. Emerging trends and research foci of oncolytic virotherapy for central nervous system tumors: a bibliometric study. *Front Immunol*. 2022:13. doi:10.3389/fimmu.2022.975695.
20. Mozaffari Nejad AS, Noor T, Munim ZH, Alikhani MY, Ghaemi A. A bibliometric review of oncolytic virus research as a novel approach for cancer therapy. *Virol j*. 2021;18(1). doi:10.1186/s12985-021-01571-7
21. Birkle C, Pendlebury DA, Schnell J, Adams J. Web of science as a data source for research on scientific and scholarly activity. *Quant Sci Stud*. 2020;1(1):363–376. doi:10.1162/qss_a_00018
22. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci*. 2004;101(suppl_1):5303–5310. doi:10.1073/pnas.0307513100
23. Fu Y, Gong C, Zhu C, Zhong W, Guo J, Chen B. Research trends and hotspots of neuropathic pain in neurodegenerative diseases: a bibliometric analysis. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1182411
24. Chen C. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. *J Am Soc Inf Sci Technol*. 2006;57 (3):359–377. doi:10.1002/asi.20317
25. Cortese S, Sabé M, Chen C, Perroud N, Solmi M. Half a century of research on attention-deficit/hyperactivity disorder: a scientometric study. *Neurosci Biobehav Rev*. 2022;140:104769. doi:10.1016/j.neubiorev.2022.104769
26. Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 Phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6(7):1003. doi:10.1001/jamaoncol.2020.1024
27. Lang FF, Conrad C, Gomez-Manzano C, et al. Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma. *J Clin Oncol*. 2018;36(14):1419–1427. doi:10.1200/jco.2017.75.8219
28. Geletneky K, Hajda J, Angelova AL, et al. Oncolytic H-1 parvovirus shows safety and signs of immunogenic activity in a first phase I/IIa glioblastoma trial. *Mol Ther*. 2017;25(12):2620–2634. doi:10.1016/j.ymthe.2017.08.016
29. Friedman GK, Johnston JM, Bag AK, et al. Oncolytic HSV-1 G207 immunovirotherapy for pediatric high-grade gliomas. *N Engl J Med*. 2021;384 (17):1613–1622. doi:10.1056/nejmoa2024947
30. O'Rourke DM, Nasrallah MP, Desai A, et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. *Sci Transl Med*. 2017;9(399). doi:10.1126/scitranslmed.aaa0984

31. Cloughesy TF, Mochizuki AY, Orpilla JR, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat Med*. 2019;25(3):477–486. doi:10.1038/s41591-018-0337-7
32. Saha D, Martuza RL, Rabkin SD. Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade. *Cancer Cell*. 2017;32(2):253–267.e5. doi:10.1016/j.ccell.2017.07.006
33. Cheema TA, Wakimoto H, Fecci PE, et al. Multifaceted oncolytic virus therapy for glioblastoma in an immunocompetent cancer stem cell model. *Proc Natl Acad Sci*. 2013;110(29):12006–12011. doi:10.1073/pnas.1307935110
34. Zemp FJ, Corredor JC, Lun X, Muruve DA, Forsyth PA. Oncolytic viruses as experimental treatments for malignant gliomas: using a scourge to treat a devil. *Cytokine Growth Factor Rev*. 2010;21(2–3):103–117. doi:10.1016/j.cytogfr.2010.04.001
35. Kanai R, Rabkin SD, Yip S, et al. Oncolytic virus-mediated manipulation of DNA damage responses: synergy with chemotherapy in killing glioblastoma stem cells. *JNCI J Natl Cancer Inst*. 2012;104(1):42–55. doi:10.1093/jnci/djr509
36. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: a new era of cancer treatment at Dawn. *Cancer Sci*. 2016;107(10):1373–1379. doi:10.1111/cas.13027
37. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. 2017;18(10):1373–1385. doi:10.1016/S1470-2045(17)30517-X
38. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. *Nat Rev Drug Discovery*. 2015;14(9):642–662. doi:10.1038/nrd4663
39. Wakimoto H, Kesari S, Farrell CJ, et al. Human glioblastoma–derived cancer stem cells: establishment of invasive glioma models and treatment with oncolytic herpes simplex virus vectors. *Cancer Res*. 2009;69(8):3472–3481. doi:10.1158/0008-5472.CAN-08-3886
40. Fares J, Ahmed AU, Ulasov IV, et al. Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a first-in-human, Phase 1, dose-escalation trial. *Lancet Oncol*. 2021;22(8):1103–1114. doi:10.1016/s1470-2045(21)00245-x
41. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N Engl J Med*. 2016;375(26):2561–2569. doi:10.1056/NEJMoa1610497
42. Andtbacka RHI, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015;33(25):2780–2788. doi:10.1200/jco.2014.58.3377
43. J GP-L, Garcia-Moure M, Labiano S, et al. Oncolytic DNX-2401 virus for pediatric diffuse intrinsic pontine glioma. *N Engl J Med*. 2022;386(26):2471–2481. doi:10.1056/NEJMoa2202028
44. Forsyth P, Roldán G, George D, et al. A phase I trial of intratumoral administration of reovirus in patients with histologically confirmed recurrent malignant gliomas. *Mol Ther*. 2008;16(3):627–632. doi:10.1038/sj.mt.6300403
45. Markert JM, Liechty PG, Wang W, et al. Phase ib trial of mutant herpes simplex virus G207 inoculated pre-and post-tumor resection for recurrent GBM. *Mol Ther*. 2009;17(1):199–207. doi:10.1038/mt.2008.228
46. Russell SJ, Peng KW, Bell JC. Oncolytic virotherapy. *Nat Biotechnol*. 2012;30(7):658–670. doi:10.1038/nbt.2287
47. Zhang T, Jiang S, Zhang L, et al. A bibliometric analysis of oncolytic virotherapy combined with immunotherapy. *Hum Vaccin Immunother*. 2024;20(1). doi:10.1080/21645515.2024.2406621
48. Ling AL, Solomon IH, Landivar AM, et al. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. *Nature*. 2023;623(7985):157–166. doi:10.1038/s41586-023-06623-2
49. Chiocca EA, Aguilar LK, Bell SD, et al. Phase IB study of gene-mediated cytotoxic immunotherapy adjuvant to up-front surgery and intensive timing radiation for malignant glioma. *J Clin Oncol*. 2011;29(27):3611–3619. doi:10.1200/jco.2011.35.5222
50. Chiocca EA, Gelb AB, Chen CC, et al. Combined immunotherapy with controlled interleukin-12 gene therapy and immune checkpoint blockade in recurrent glioblastoma: an open-label, multi-institutional phase I trial. *Neuro oncol*. 2022;24(6):951–963. doi:10.1093/neuonc/noab271
51. Nakamura H, Takami H, Yanagisawa T, et al. The Japan society for neuro-oncology guideline on the diagnosis and treatment of central nervous system germ cell tumors. *Neuro oncol*. 2022;24(4):503–515. doi:10.1093/neuonc/noab242
52. Saha D, Wakimoto H, Peters CW, Antoszczyk SJ, Rabkin SD, Martuza RL. Combinatorial effects of VEGFR kinase inhibitor axitinib and oncolytic virotherapy in mouse and human glioblastoma stem-like cell models. *Clin Cancer Res*. 2018;24(14):3409–3422. doi:10.1158/1078-0432.ccr-17-1717
53. Todo T, Martuza RL, Rabkin SD, Johnson PA. Oncolytic herpes simplex virus vector with enhanced MHC class I presentation and tumor cell killing. *Proc Natl Acad Sci*. 2001;98(11):6396–6401. doi:10.1073/pnas.101136398
54. Otsuki A, Patel A, Kasai K, et al. Histone deacetylase inhibitors augment antitumor efficacy of herpes-based oncolytic viruses. *Mol Ther*. 2008;16(9):1546–1555. doi:10.1038/mt.2008.155
55. Wojton J, Kaur B. Impact of tumor microenvironment on oncolytic viral therapy. *Cytokine Growth Factor Rev*. 2010;21(2–3):127–134. doi:10.1016/j.cytogfr.2010.02.014
56. Thaci B, Ahmed AU, Ulasov IV, et al. Pharmacokinetic study of neural stem cell-based cell carrier for oncolytic virotherapy: targeted delivery of the therapeutic payload in an orthotopic brain tumor model. *Cancer Gene Ther*. 2012;19(6):431–442. doi:10.1038/cgt.2012.21
57. Ahmed AU, Thaci B, Tobias AL, et al. A preclinical evaluation of neural stem cell–based cell carrier for targeted antiglioma oncolytic virotherapy. *JNCI J Natl Cancer Inst*. 2013;105(13):968–977. doi:10.1093/jnci/djt141
58. Kambara H, Okano H, Chiocca EA, Saeki Y. An oncolytic HSV-1 mutant expressing ICP34.5 under control of a nestin promoter increases survival of animals even when symptomatic from a brain tumor. *Cancer Res*. 2005;65(7):2832–2839. doi:10.1158/0008-5472.can-04-3227
59. Lubin JA, Zhang RR, Kuo JS. Zika virus has oncolytic activity against glioblastoma stem cells. *Neurosurgery*. 2018;82(5):E113–E114. doi:10.1093/neuros/nyy047
60. Zrachia A, Dobroslav M, Blass M, et al. Infection of glioma cells with sindbis virus induces selective activation and tyrosine phosphorylation of protein kinase C δ. *J Biol Chem*. 2002;277(26):23693–23701. doi:10.1074/jbc.m111658200
61. Fucikova J, Kepp O, Kasikova L, et al. Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death Dis*. 2020;11(11). doi:10.1038/s41419-020-03221-2
62. Workenhe ST, Mossman KL. Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies. *Mol Ther*. 2014;22(2):251–256. doi:10.1038/mt.2013.220
63. Sahu U, Mullarkey MP, Murphy SA, et al. IDH status dictates oHSV mediated metabolic reprogramming affecting anti-tumor immunity. *Nat Commun*. 2025;16(1). doi:10.1038/s41467-025-58911-2
64. Chen Q, Wu J, Ye Q, et al. Treatment of human glioblastoma with a live attenuated zika virus vaccine candidate. *MBio*. 2018;9(5). doi:10.1128/mbio.01683-18

65. Pérez-Ruiz E, Etxeberria I, Rodriguez-Ruiz ME, Melero I. Anti-CD137 and PD-1/PD-L1 antibodies en route toward clinical synergy. *Clin Cancer Res*. 2017;23(18):5326–5328. doi:10.1158/1078-0432.ccr-17-1799
66. Azambuja JH, Gelsleichter NE, Beckenkamp LR, et al. CD73 downregulation decreases In vitro and In vivo glioblastoma growth. *Mol Neurobiol*. 2019;56(5):3260–3279. doi:10.1007/s12035-018-1240-4
67. Nassiri F, Patil V, Yefet LS, et al. Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial. *Nat Med*. 2023;29(6):1370–1378. doi:10.1038/s41591-023-02347-y
68. Samson A, Scott KJ, Taggart D, et al. Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade. *Sci Transl Med*. 2018;10(422):eaam7577. doi:10.1126/scitranslmed.aam7577
69. Singh A, Kanda A, Kanda J. Recent approaches on oncolytic viruses, aptamers, TTFields and PersonalizedTreatment used for the management of glioblastoma: a comprehensive review. *Anticancer Agents Med Chem*. 2025;25(19):1485–1505. doi:10.2174/0118715206364677250401190214
70. Cloughesy TF, Landolfi J, Vogelbaum MA, et al. Durable complete responses in some recurrent high-grade glioma patients treated with Toca 511 + Toca FC. *Neuro oncol*. 2018;20(10):1383–1392. doi:10.1093/neuonc/noy075
71. Durham PG, Butnariu A, Alghorazi R, Pinton G, Krishna V, Dayton PA. Current clinical investigations of focused ultrasound blood-brain barrier disruption: a review. *Neurotherapeutics*. 2024;21(3):e00352. doi:10.1016/j.neurot.2024.e00352
72. Giles B, Nakhjavani M, Wiesa A, Knight T, Shigdar S, Samarasinghe RM. Unravelling the glioblastoma tumour microenvironment: can aptamer targeted delivery become successful in treating brain cancers? *Cancers*. 2023;15(17):4376. doi:10.3390/cancers15174376
73. Hamad A, Yusubalieva GM, Baklaushev VP, Chumakov PM, Lipatova AV. Recent developments in glioblastoma therapy: oncolytic viruses and emerging future strategies. *Viruses*. 2023;15(2):547. doi:10.3390/v15020547
74. Joseph JV, Blaavand MS, Daubon T, Kruyt FA, Thomsen MK. Three-dimensional culture models to study glioblastoma — current trends and future perspectives. *Curr Opin Pharmacol*. 2021;61:91–97. doi:10.1016/j.coph.2021.08.019
75. Stavrakaki E, Dirven CMF, Lamfers MLM. Personalizing oncolytic virotherapy for glioblastoma: in search of biomarkers for response. *Cancers*. 2021;13(4):614. doi:10.3390/cancers13040614