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Mapping and Visualization of Global Research on Bispecific Antibodies in Solid Tumors: A Bibliometric Analysis (2006–2025)

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Abstract: Background: Although bispecific antibodies (BsAbs) hold promising therapeutic prospects in solid tumors, there is scarce bibliometric analysis on this field. This study aimed to systematically map the research landscape, identify key trends, and highlight future directions for BsAb research in solid tumors. Methods: Literature of BsAb development for solid tumors was retrieved from Web of Science Core Collection published between 2006 and 2025. Publication distribution, research trends and hotspots were analyzed and visualized by VOSviewer, CiteSpace and the R package "bibliometrix". Results: Overall, we identified 3632 publications stemming from a fast-growing field currently strongly influenced by the United States and China, with Memorial Sloan Kettering Cancer Center and National Cancer Institute the most productive research centers, Front Immunol the most productive journal and J Clin Oncol the most cited. The dominant research topics that appeared from keyword analysis are bispecific antibody, immunotherapy, targeted therapy, non-small cell lung cancer, and EGFR. Conclusion: This study documents the evolution of BsAb research, from basic science to clinical translational research in solid tumors. The research in this field is highly mature at this point, with emphasis on the targeting of specific tumor types and specific antigens. In order to further push forward the frontier, greater international and subfield collaborations, as well as larger-scale clinical trials targeting broader indications, overcoming resistant mechanisms and combination strategies are necessary.

Keywords: Bibliometric analysis; Bispecific antibody; Solid tumors; Immunotherapy; Targeted therapy

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1. Introduction

Although approaches for treating solid tumors have advanced dramatically in the past decades, there still exist significant challenges. Existing systemic therapeutic methods such as chemotherapy, targeted therapy, and immune-based therapy are still likely to yield unsatisfying efficacies, severe side effects and primary

or acquired resistance [1–3], which demands innovative therapeutic approaches. The recent advancement of Bispecific antibodies (BsAbs) represents a promising avenue to overcome these drawbacks.

The concept of BsAbs was first suggested by Nisonoff and his colleagues at the beginning of the 1960s [4], but the technological realization faced significant difficulties [5]. The first generation of BsAbs was produced either by chemical linking or by hybrid-hybridoma (quadroma) technology, which suffered a lack of stability, low titer and high immunogenicity [6,7]. The key advance was with the introduction of developments in molecular engineering through genetic engineering, which allows the accurate pairing of heavy and light chains of an antibody, thus forming a stable bispecific structure [8,9]. In recent decades, increasing research has focused on the development of BsAb for solid tumors [10]. BsAbs are genetically engineered proteins that bind two different antigens or two epitopes on the same antigen sequentially or simultaneously and thus can potentially initiate mechanisms beyond the simple additive activity of two mAbs [11]. Compared to mAbs, BsAbs offer the advantage of enhanced targeting with dual specificity, resulting in higher binding efficiency, reduced susceptibility to resistance, and unique functions, including direct engagement of T cells to selectively kill tumor cells [12]. Meanwhile, the single antibody architecture of BsAbs means less Fc fragment exposure, thus reducing their adverse effects.

BsAbs have changed the treatment paradigms of hematological malignancies in the past decade [13,14] with the approval of T-cell engager blinatumomab for acute lymphoblastic leukemia [15]. Nevertheless, their clinical use in solid tumors is rather limited due to several confounding factors: the immunosuppressive tumor microenvironment (TME) inhibiting T-cell activity, low density of tumor-antigens combined with their expression in normal tissues (on-target/off-tumor effects), difficulty of drug penetration caused by stromal barriers, and resistance mechanisms caused by the loss of antigens [16]. Nevertheless, rapid progress has been achieved. As of October 2025, eight BsAbs have been approved to treat solid tumors and four of them were approved in 2024 [2,17–19], which indicates a recent blossom in clinical success.

Although BsAbs feature attractive characteristics for their roles in treating solid tumors, there are unanswered questions regarding the mechanisms involved in their boost of immune system activity against solid tumors, as well as the resolutions to on-target/off-tumor effects. Furthermore, the trajectory and the research hotspot of BsAbs in solid tumors have not yet been analyzed by bibliometric analysis. Based on these, the purpose of our study is to analyze the research and development of BsAbs in solid tumors and to describe research hotspots, keywords, and collaborators in this field. This study was conducted based on bibliometric analysis, a method that enables us to quantitatively evaluate scientific papers [20] through standard data collecting and mining from publications, citations and research collaborations on BsAbs and solid tumors. We aim to provide a comprehensive overview of research in this field, as insights may emerge that guide forthcoming research and clinical practice.

2. Materials and methods

2.1. Data source and search strategy

The literature search was conducted in the Web of Science Core Collection (WoSCC). The searching time frame was around 20 years (January 1, 2006–November 7, 2025). The whole process of data extraction and export was performed in one day (November 7, 2025) to reduce possible discrepancies due to daily database updates. The search terms were as follows: TS = (*cancer* OR *neoplas* OR *tumo* OR *carcinoma* OR *adenocarcinoma* OR *metasta* OR *malignan* OR *sarcoma* OR *melanoma*

OR *oncolog*) AND TS = (bispecific antibod* OR bispecific monoclonal antibod* OR bsab* OR bifunctional antibod* OR bifunctional monoclonal antibod* OR T-cell engager* OR T cell engager* OR Catumaxomab OR Amivantamab OR Tebentafusp OR Cadonilimab OR Tarlatamab OR Ivonescimab OR Zanidatamab OR Zenocutuzumab) NOT TS = (leukemia* OR leukaemia* OR lymphoma* OR myeloma* OR myeloproliferative disorder* OR hematologic* OR haematologic* OR blood cancer*). The inclusion of publications was restricted to articles and reviews published in English. The literature search and screening processes are shown in **Figure 1**.

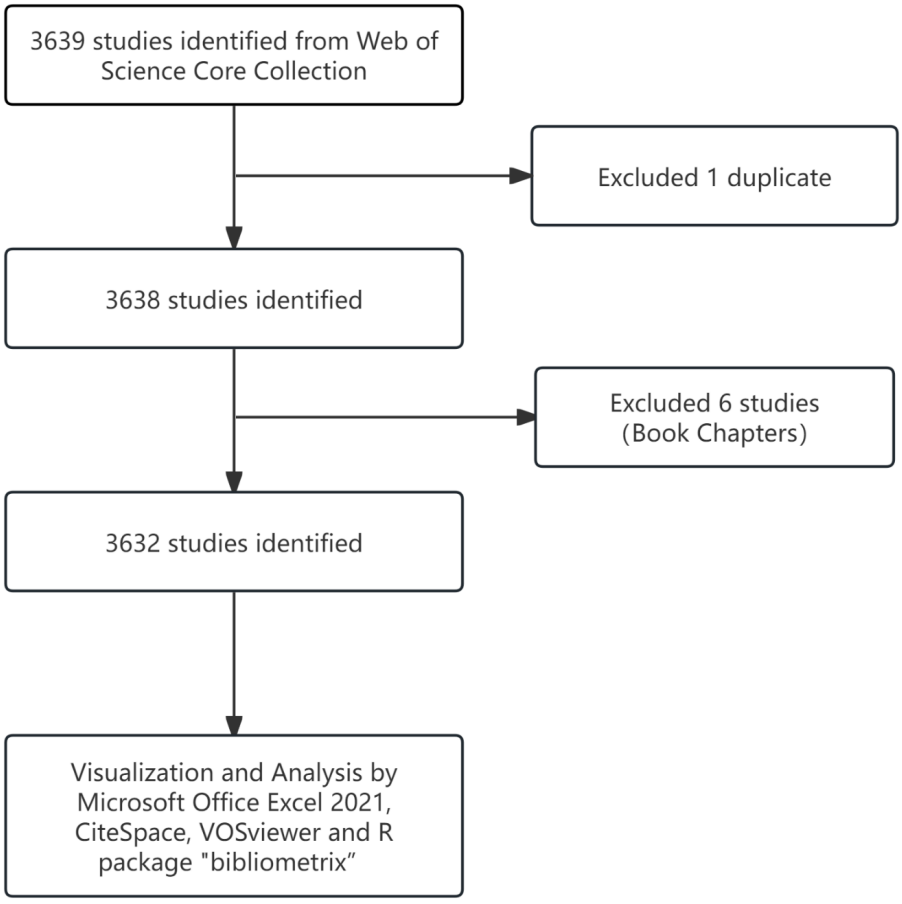

Figure 1. Flowchart illustrating the search strategy and selection process.

2.2. Bibliometric analysis and visualization

The bibliometric analysis was performed using VOSviewer (version 1.6.20), CiteSpace (version 6.2.R3), and the R package "bibliometrix" (version 4.2.1). VOSviewer was used to generate collaboration, co-citation, and co-occurrence networks for countries, institutions, authors, journals, and keywords. In the generated maps, the size of a node corresponds to a metric (e.g., publication count), its color denotes a cluster classification, and the thickness of the connecting lines indicates the strength of the relationship (e.g., collaboration or co-citation frequency). CiteSpace was used to generate a dual-map overlay of journals and to identify references and keywords with citation bursts. The "bibliometrix" package (https://www.bibliometrix.org) was used for

the analysis of thematic evolution and the construction of a global publication distribution network. Journal metrics, including the quartile and impact factor, were obtained from Journal Citation Reports (JCR) 2024. Microsoft Office Excel 2021 was used for quantitative analysis of annual publication trends.

3. Results

3.1. Annual publication trend

The study obtained 3632 publications in total from the database, containing 2600 articles and 1032 reviews. The number of annual publications showed an upward trend, increasing from 32 in 2006 to more than 100 in 2015 (**Figure 2**). Following a period of gradual growth, a sharp increase occurred in 2019, after which the publication counts rose dramatically to a peak of 604 in 2025. The growth curve was well fitted with a polynomial ($R^2 = 0.9712$) in Microsoft Office Excel 2021, which verified this positive correlation between the publication year and output. This quantitative assessment confirms a significant trend statistically and illustrates a growing interest in BsAbs for solid tumors over recent years.

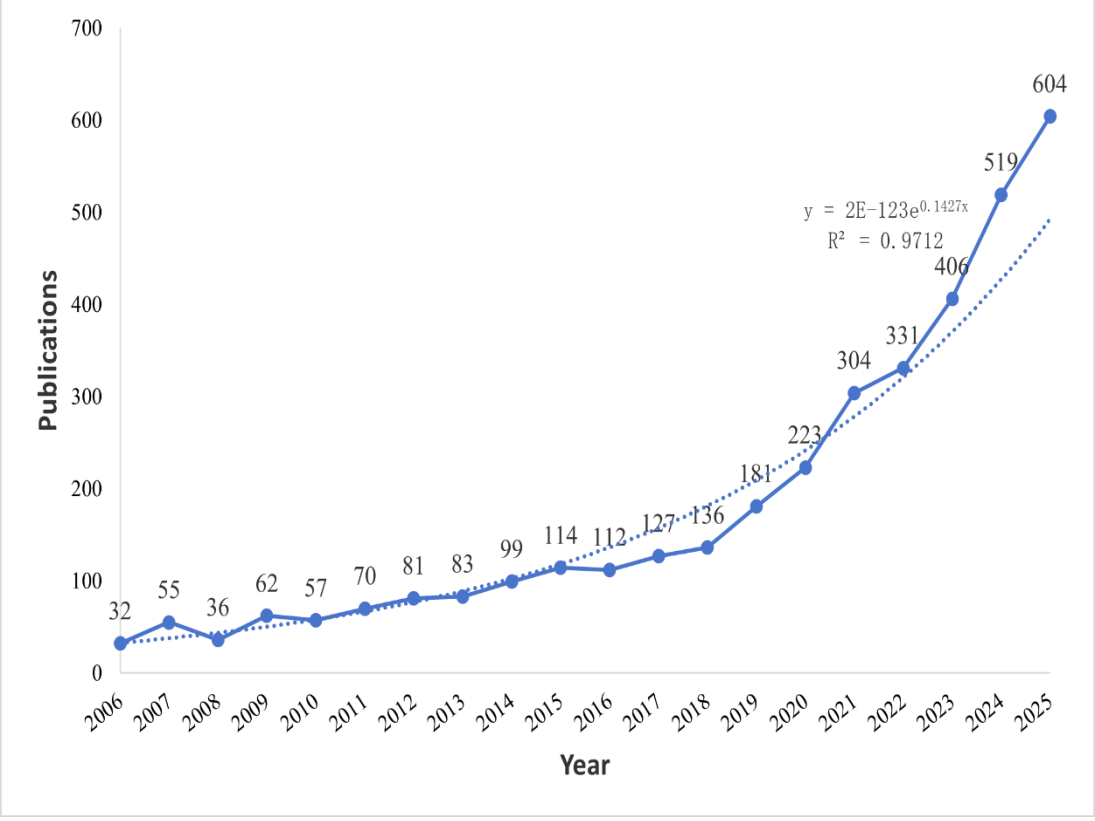

Figure 2. Annual output of bispecific antibody research for solid tumors.

3.2. International contributions by country/region and institution analyses

Publications originated from 78 countries/regions and 4375 institutions. The top 10 countries/regions are from Asia, Europe and North America, mainly Europe (n = 6) and Asia (n = 3) (**Table 1**). The United States (US) was the biggest contributor (1400 publications, 38.5%), followed by China (903, 24.9%), Germany (511, 14.1%) and the United Kingdom (229, 6.3%). Notably, the US and China account for 63.4% of the total publications. The collaborative network was generated according to the publication amount and inter-country

collaborations, with a threshold of a minimum of 5 publications per country/region (**Figure 3A**). The network includes a total of 51 countries/ regions, which shows a high degree of international cooperation (**Figure 3B**). For instance, the US has been working closely with nations like China, Germany, and South Korea. China's cooperative engagements, though globally extensive, are relatively less intensive.

Table 1. Top 10 countries and institutions in bispecific antibody research for solid tumors

Country	Counts	Institution	Counts
The US	1400	Memorial Sloan Kettering Cancer Center (The US)	102
China	903	National Cancer Institute (The US)	61
Germany	511	Sun Yat-Sen University (China)	58
The United Kingdom	229	Huazhong University of Science and Technology (China)	57
France	201	The University of Texas MD Anderson Cancer Center (The US)	56
Japan	197	Zhejiang University (China)	54
Switzerland	184	Chinese Academy of Sciences (China)	52
Netherlands	168	Harvard Medical School (The US)	50
South Korea	165	German Cancer Research Center (Germany)	50
Italy	164	Shanghai Jiao Tong University (China)	49

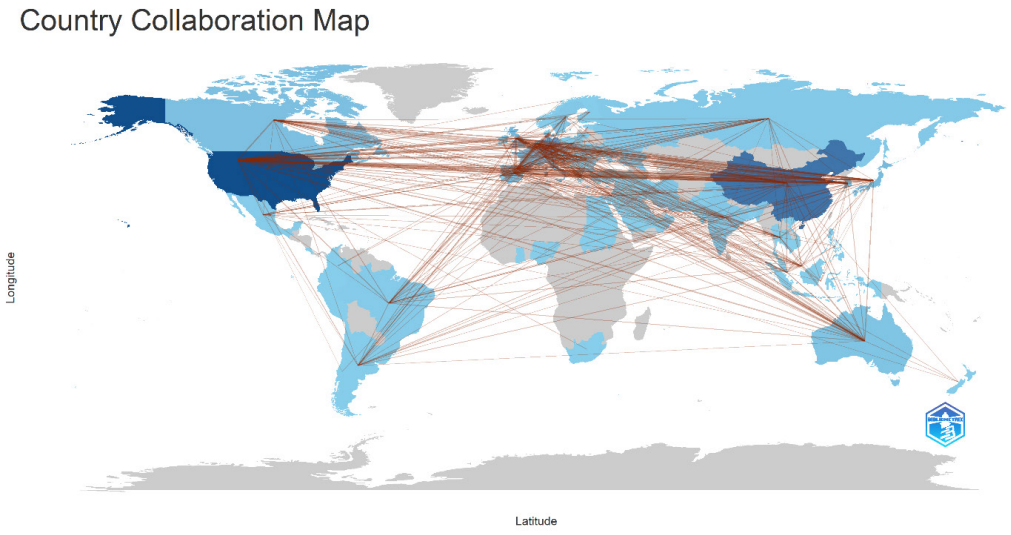

Figure 3A. Geographical distribution of bispecific antibody research in solid tumors.

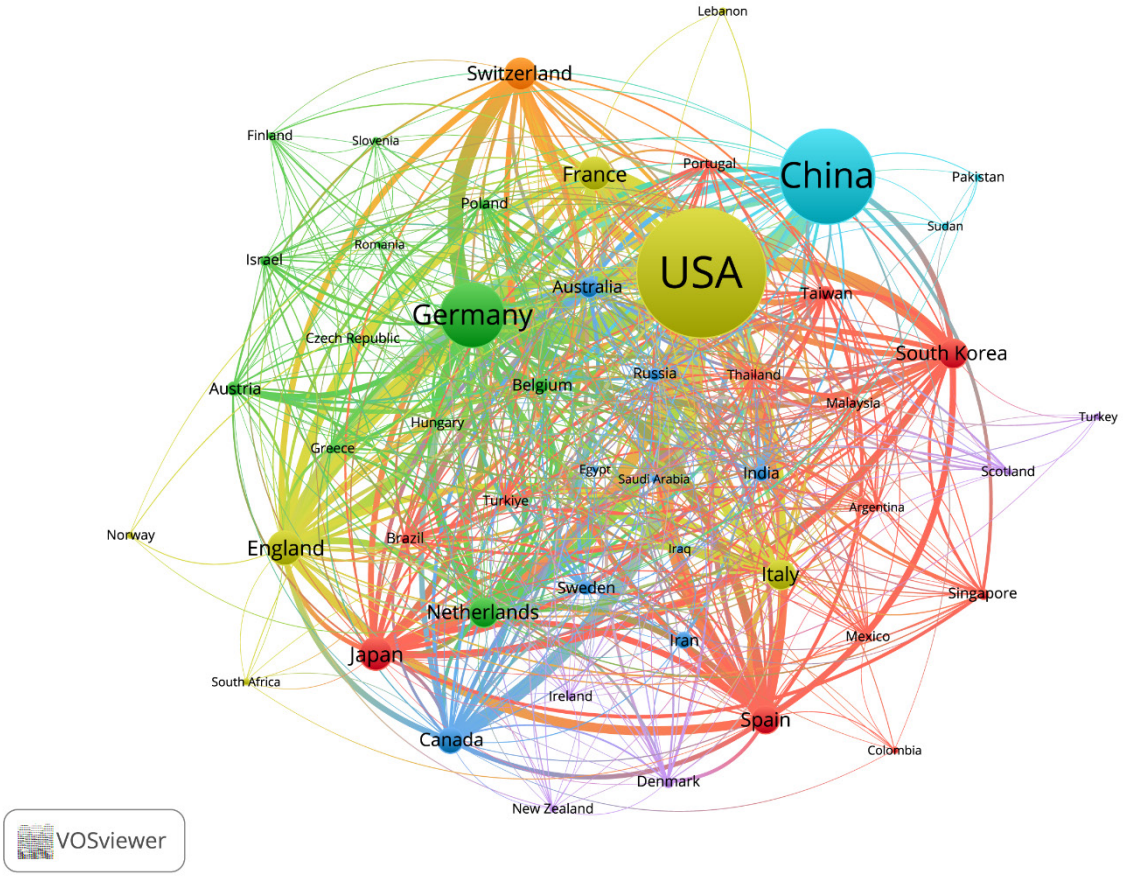

Figure 3B. Visualization of countries on bispecific antibody research in solid tumors.

Among the top 10 institutions, the majority were distributed between two countries, with nine located in either China or the US. Memorial Sloan Kettering Cancer Center (n = 102, 2.8%), National Cancer Institute (n = 61, 1.7%), and Sun Yat-sen University (n = 58, 1.6%) were the top three institutions in terms of the number of relevant publications. We selected a subset of 48 institutions, with a minimum of three publications per institution, for further analysis. A collaborative network was then built to visualize the publication relationships and number of co-authorships among institutions (**Figure 4**). The figure clearly shows that institutions have extensive cooperation, with Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center at the core of the collaborative network. In addition, solid collaborations exist between academic, clinical and industry institutions (Genentech, Amgen, Roche Innovation Center), pushing BsAb research forward in both fundamental science and clinical practice.

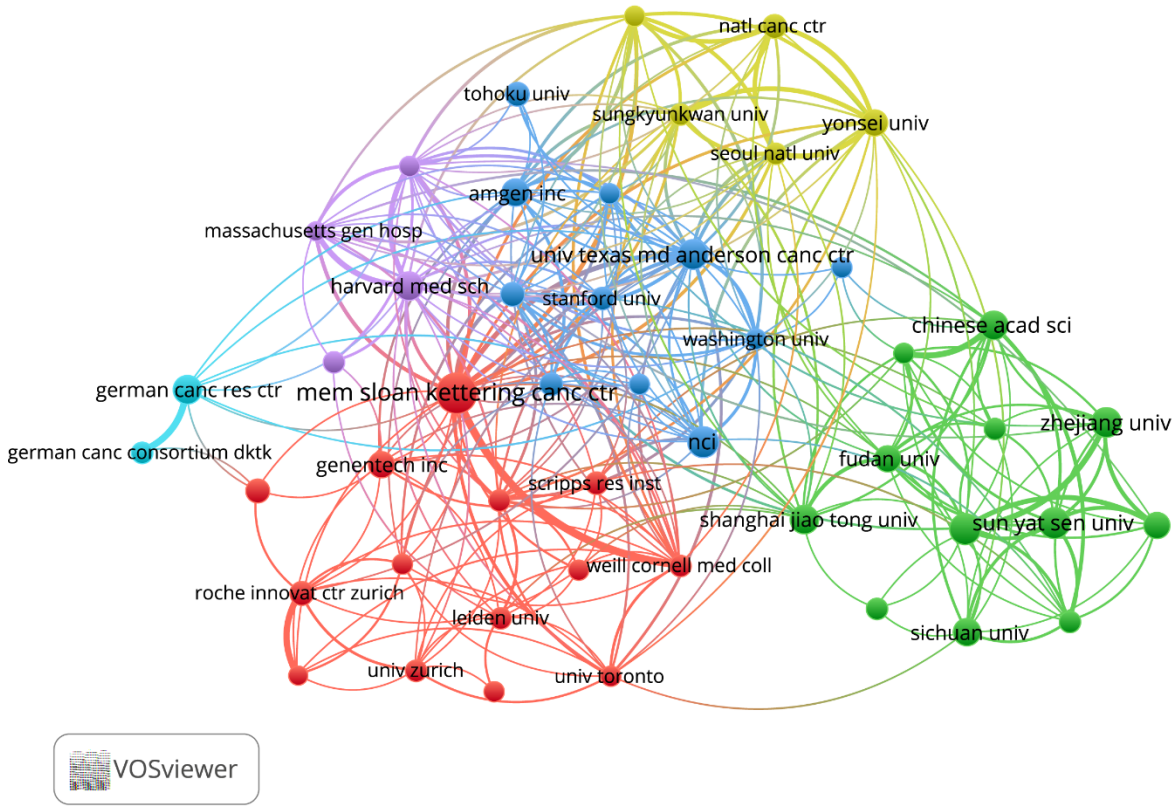

Figure 4. Visualization of institutions on bispecific antibody research in solid tumors.

3.3. Journals and co-cited journals

An analysis of the scholarly landscape identified 836 journals publishing on BsAbs research in solid tumors. The top 10 journals and the most cited journals are listed in **Table 2**. The influence of the journals was evaluated based on the most recent Journal Impact Factor (IF) and JCR quartile retrieved from WoSCC. The leading journal in terms of the number of relevant publications was *Front Immunol* (n = 137, 16.4%), followed by *MAbs* (n = 115, 13.8%), and *Cancers (Basel)* (n = 83, 9.9%). Of the top 10 most productive journals, *Clin Cancer Res* (IF = 10.2), *MAbs* (IF = 7.3), and *Oncoimmunology* (IF = 6.3) had the highest IF according to JCR 2024. The journal co-occurrence network was mapped for 48 journals that published a minimum of 14 relevant articles (**Figure 5A**). This network illustrates active citation relationships, notably positioning *Front Immunol* as a central hub connected to journals such as *MAbs* and *J Immunother Cancer*.

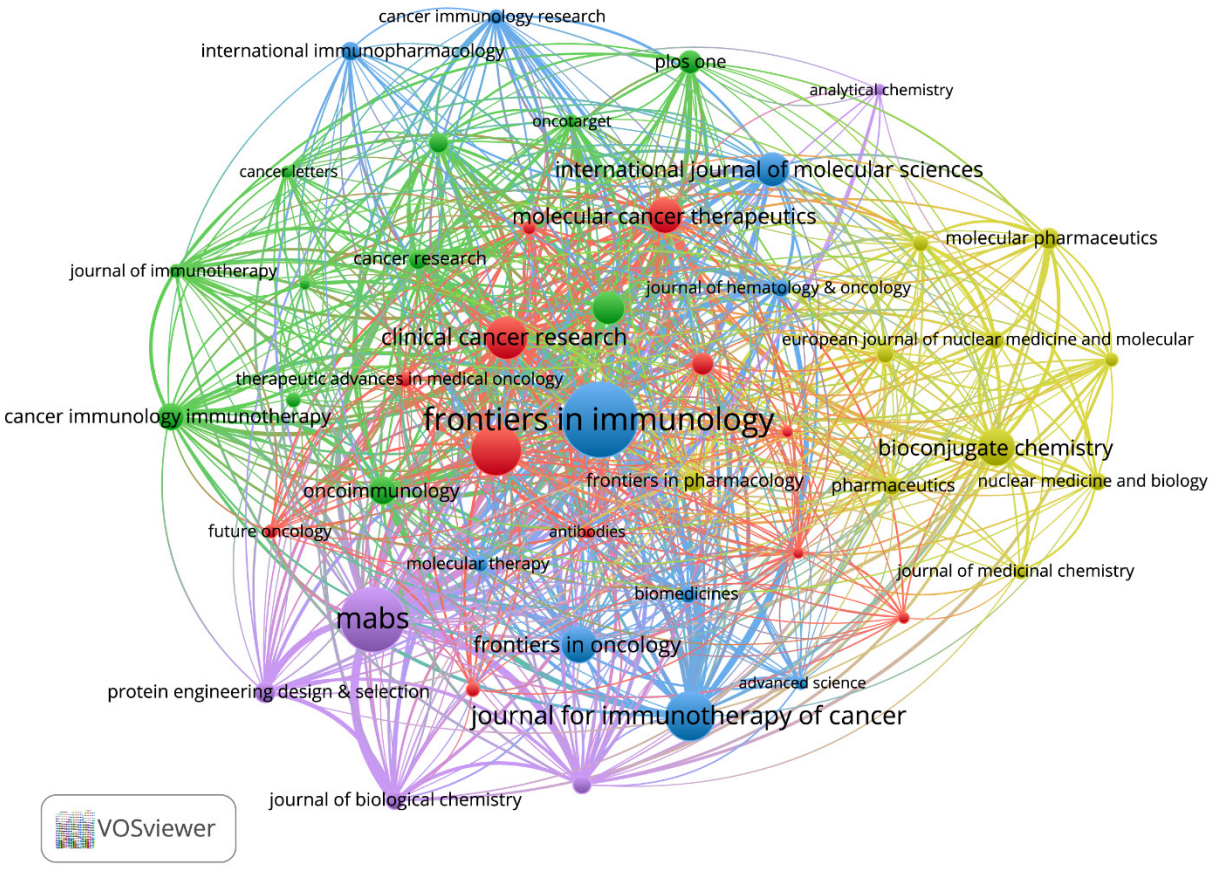

Figure 5A. Visualization of journals on bispecific antibody research in solid tumors.

As shown in **Table 2**, all of top 10 co-cited journals were co-cited over 3000 times, while the top three were *J Clin Oncol* (8998), *Clin Cancer Res* (7698), and *Cancer Res* (6823). Most of these journals were highly influential, as 90% of them were ranked in the JCR Q1 quartile and 60% with IF > 10, led by *N Engl J Med* (IF = 78.5), *Ann Oncol* (IF = 65.4), and *Nature* (IF = 48.5). Figure 5B displays the co-citation network, in which journals that have been co-cited over 480 times are included. The analysis demonstrates a highly integrated landscape of BsAb research. Among the three clusters, journals in the green cluster primarily focus on fundamental research, such as tumor biology and biotechnology, aiming to investigate the mechanisms of BsAbs and drug development. Journals in the blue cluster, predominantly clinical oncology publications, serve to synthesize data from landmark clinical trials and provide clinical validation for the research. The red cluster consists of journals focused on cancer immunology and immunotherapy, bridging the fundamental immunology with the application of BsAbs in solid tumor treatment. This visualization shows that *J Clin Oncol* demonstrates significant co-citation, frequently co-cited with journals such as *Clin Cancer Res*, *N Engl J Med* and *Ann Oncol*.

Table 2. Top 10 journals and co-cited journals on bispecific antibody research in solid tumors

Journal	Count	IF (2024)	JCR (2024)	Journals	Total Citations	IF (2024)	JCR (2024)
Front Immunol	137	5.9	Q1	J Clin Oncol	8998	41.9	Q1
MAbs	115	7.3	Q1	Clin Cancer Res	7698	10.2	Q1
Cancers (Basel)	83	4.4	Q2	Cancer Res	6823	16.1	Q1
Clin Cancer Res	67	10.2	Q1	N Engl J Med	5320	78.5	Q1
Bioconjug Chem	57	3.9	Q1	Proc Natl Acad Sci U S A	4713	9.1	Q1
Front Oncol	56	3.3	Q2	Nature	3563	48.5	Q1
Mol Cancer Ther	53	5.5	Q1	Ann Oncol	3545	65.4	Q1
Int J Mol Sci	51	4.9	Q1	Front Oncol	3294	5.9	Q1
Sci Rep	50	3.9	Q1	Mabs	3152	7.3	Q1
Oncoimmunology	40	6.3	Q1	J Immunol	3149	3.4	Q2

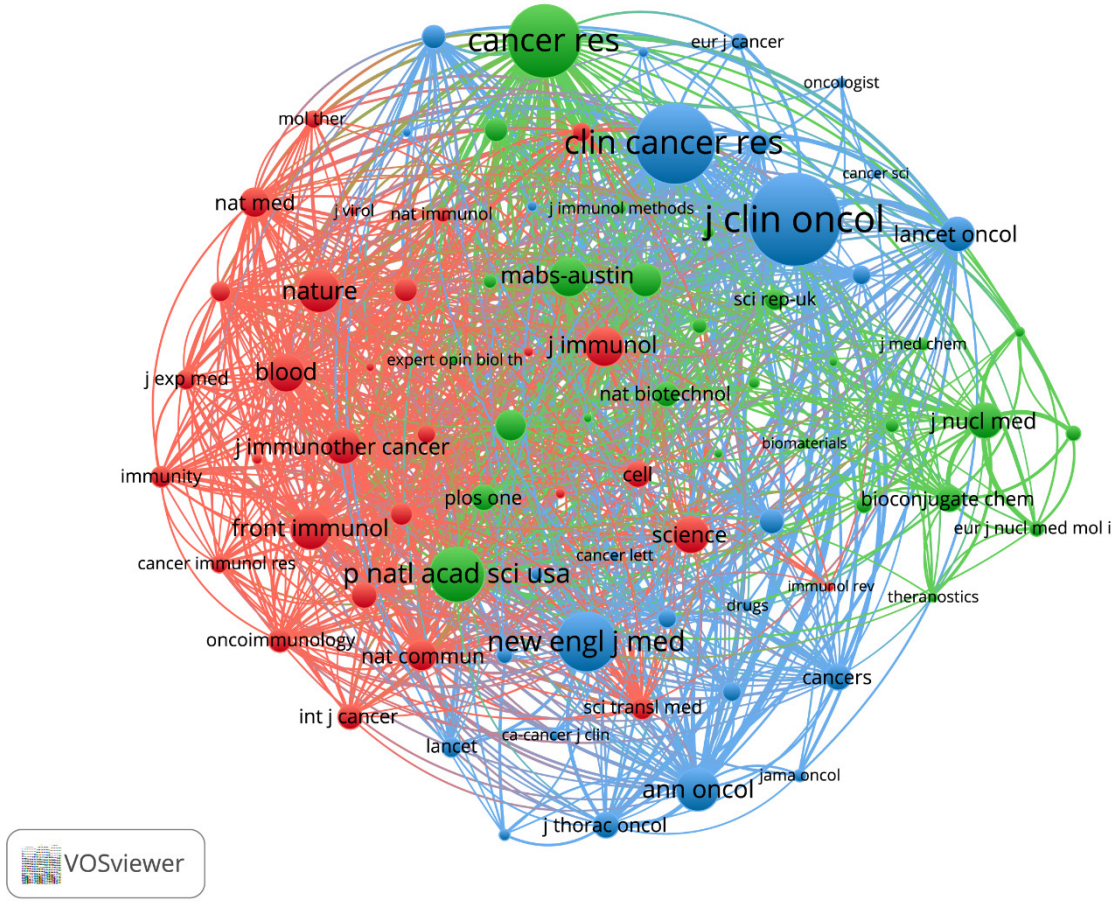

Figure 5B. Visualization of co-cited journals on bispecific antibody research in solid tumors.

The dual-map overlay of journals depicts the citation relationships and co-citation patterns, with citing journal clusters on the left and cited journal clusters on the right [21]. **Figure 6** illustrates three primary citation pathways. Research originating in molecular, biological, and genetic journals was primarily cited by work in

the molecular, biological, immunology, as well as medical and clinical fields. Similarly, articles published in health, nursing, and medical journals were predominantly cited by medical and clinical publications.

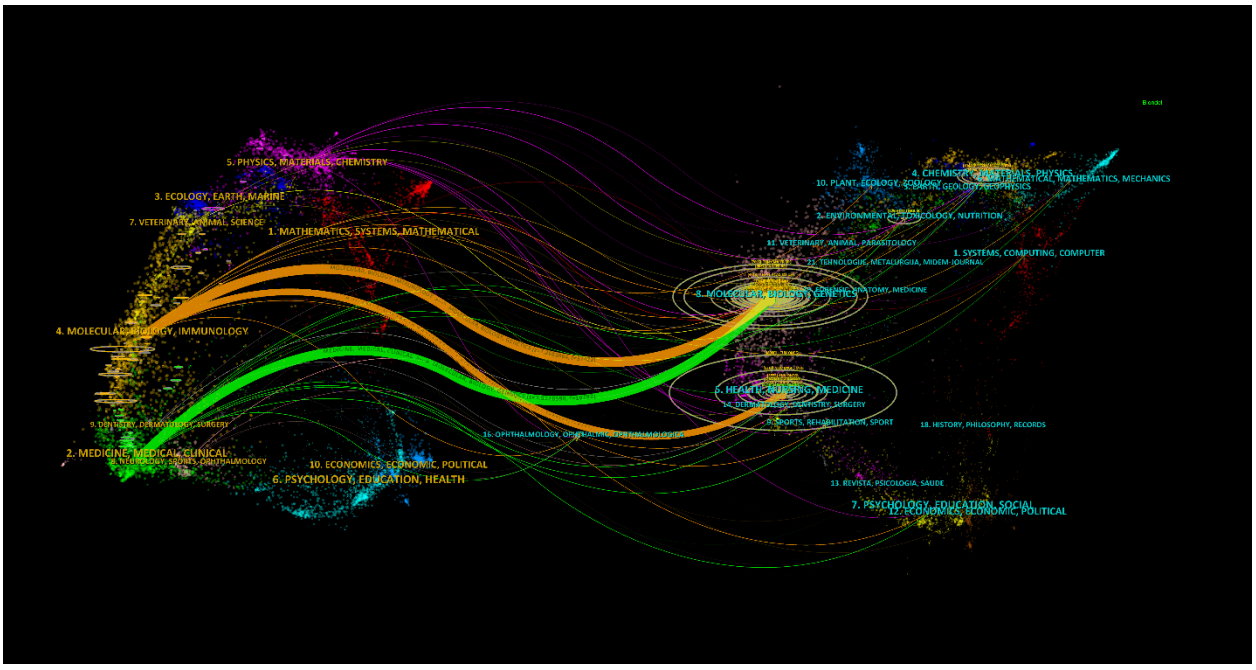

Figure 6. Dual-map overlay of journals on bispecific antibody research in solid tumors.

3.4. Authors and co-cited authors

A total of 20928 authors contributed to research on BsAbs in solid tumors. The top 10 most prolific authors each published over 20 relevant articles, with the top five being Christian Klein, Ryutaro Asano, Izumi Kumagai, Roland E. Kontermann, and Byoung Chul Cho (**Table 3**). A co-authorship network was constructed based on authors with a minimum of eight publications (**Figure 7A**). In the field of BsAb therapy for solid tumors, several distinct collaborative clusters have been formed around the aforementioned five core authors. Within these clusters, robust collaborative relationships exist among scholars, while collaborative ties of varying intensities are also present beyond these subnetworks. The cluster centered around Jessica C Hassel exhibits limited collaboration with other clusters, with its research primarily focusing on tebentafusp for uveal melanoma.

Among the 79691 co-cited authors identified, six were co-cited more than 250 times (**Table 3**). Aran F. Labrijn was the most frequently co-cited author (438 times), followed by Roland E. Kontermann (380 times) and Ulrich Brinkmann (272 times). Authors with at least 142 co-citations were included in the co-citation network analysis (**Figure 7B**). The co-citation network showed four closely related clusters: a red cluster led by Aran F. Labrijn and Roland E.Kontermann; a blue cluster centered on Pinky Sharma; a yellow cluster represented by Jing Li; and a green cluster with the core being Byoung Chul Cho.

Table 3. Top 10 authors and co-cited authors on bispecific antibody research in solid tumors

Authors	Publications	Co-cited Authors	Citations
Christian Klein	45	Aran F Labrijn	438
Ryutaro Asano	35	Roland E Kontermann	380
Izumi Kumagai	34	Ulrich Brinkmann	272
Roland E Kontermann	31	Byoung Chul Cho	268
Byoung Chul Cho	28	Patrick A Baeuerle	259
Pablo Umana	26	Jing Li	255
Wei Li	23	Luis Paz-Ares	246
Mitsuo Umetsu	22	Ming Yi	233
Jing Zhang	22	Pinky Sharma	217
Horst Lindhofer	22	Christian Klein	212

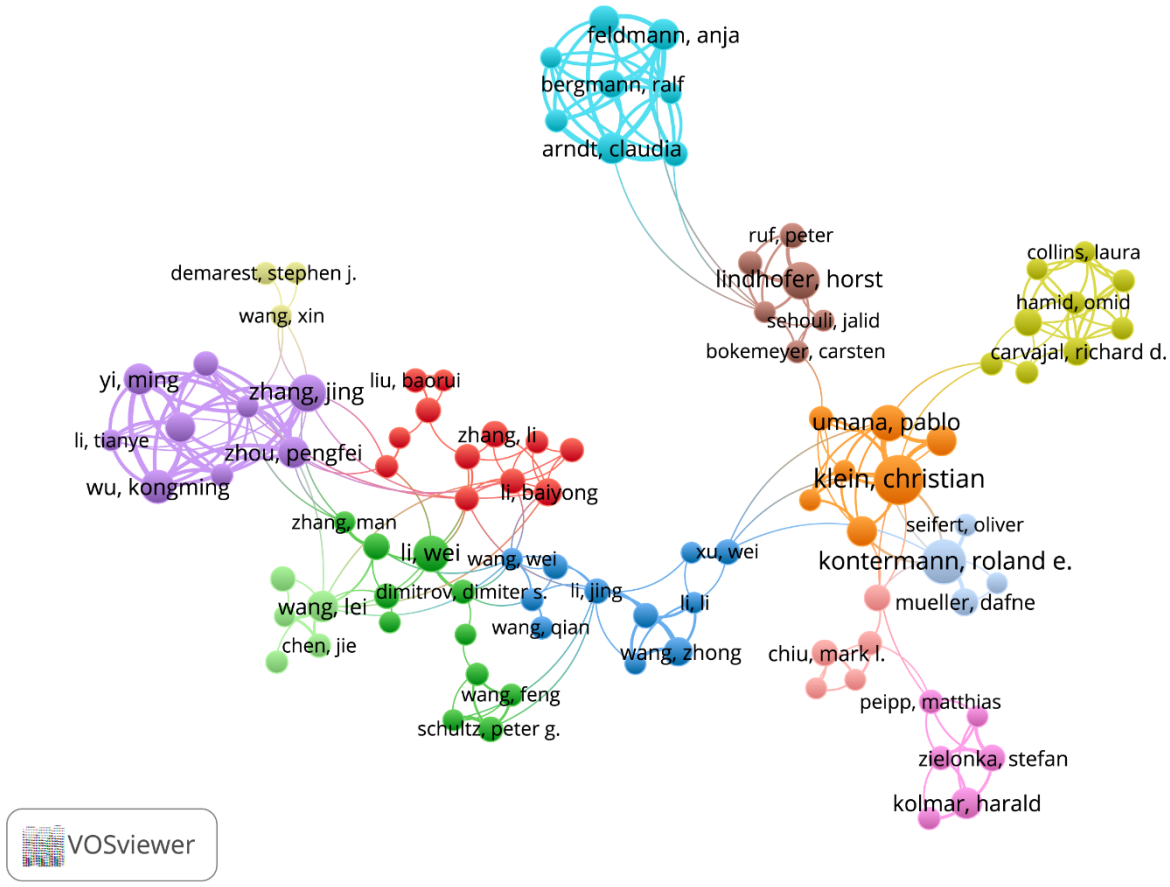

Figure 7A. Visualization of authors on bispecific antibody research in solid tumors.

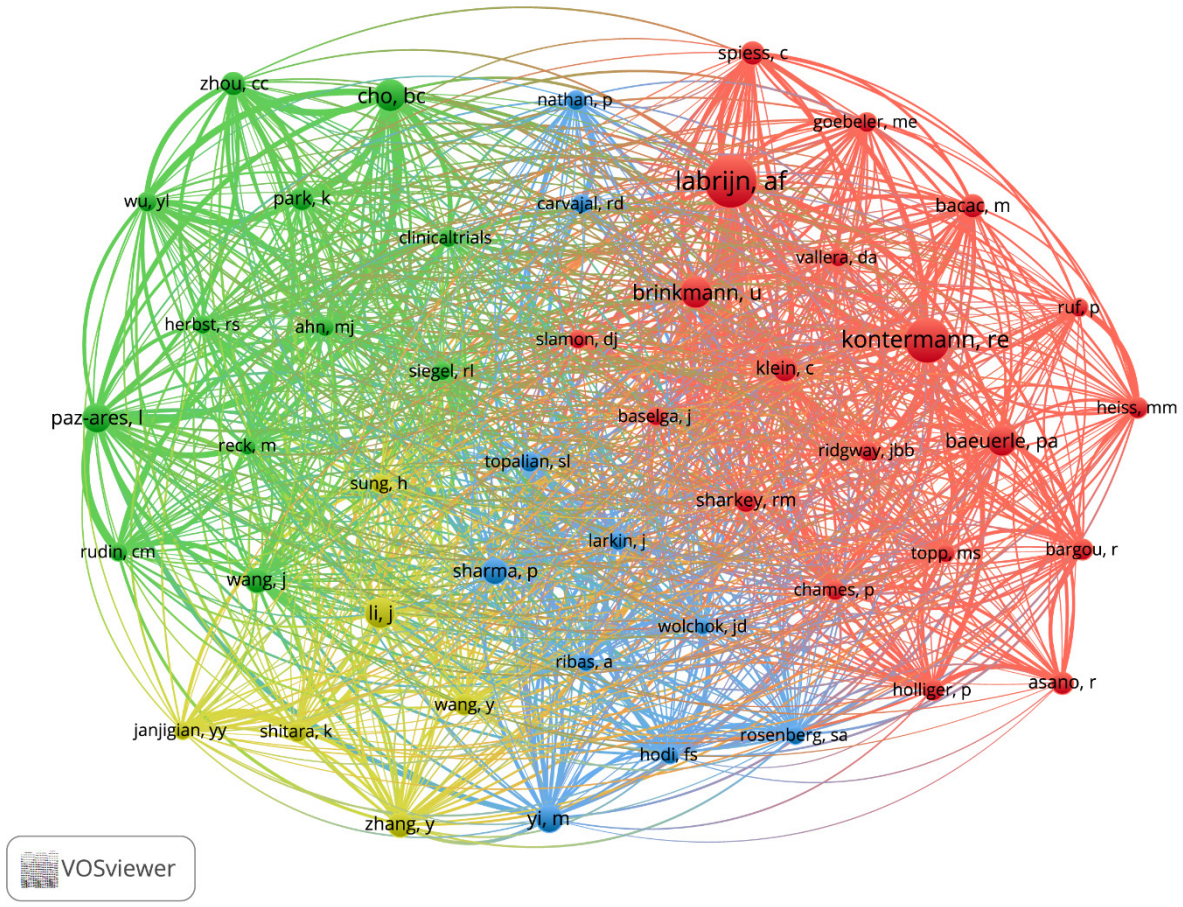

Figure 7B. Visualization of co-cited authors on bispecific antibody research in solid tumors.

3.5. Co-cited references

The analysis included the 132919 co-cited references during the last two decades of studies related to BsAbs for solid tumors. The top 10 references were co-cited 124 to 261 times (**Table 4**). The co-citation threshold was set at 77 to generate the co-citation network map (**Figure 8**), identifying several landmark publications serving to build basic knowledge of BsAbs. Articles by John B. B. Ridgway (1996), Ulrich Brinkmann (2017), and Aran F Labrijn (2019) demonstrated the highest co-citation frequencies, reflecting these authors' significant contributions to the structural engineering and clinical translation of BsAbs. Four major thematic clusters were identified through reference cluster analysis, including "Foundational research in antibody technology and biopharmaceuticals", "Clinical translation of BsAbs", "Catumaxomab", and "Amivantamab". The clear group structure and high overlap between fields suggest that molecular engineering, immunotherapy and targeted therapy are tightly integrated.

Table 4. Top 10 co-cited references on bispecific research in solid tumors

Co-cited references	Citations
Labrijn AF, 2019, Nat Rev Drug Discov, v18, p585 [22]	261
Brinkmann U, 2017, Mabs-Austin, v9, p182 [12]	224
Ridgway JBB, 1996, Protein Eng, v9, p617 [23]	169
Sung H, 2021, Ca-Cancer J Clin, v71, p209 [24]	154

Co-cited references	Citations
Nathan P, 2021, New Engl J Med, v385, p1196 [25]	144
Park K, 2021, J Clin Oncol, v39, p3391[26]	143
Baeuerle PA, 2009, Cancer Res, v69, p4941 [1]	142
Spiess C, 2015, Mol Immunol, v67, p95 [7]	134
Kontermann RE, 2015, Drug Discov Today, v20, p838 [27]	131
Merchant AM, 1998, Nat Biotechnol, v16, p677 [28]	124

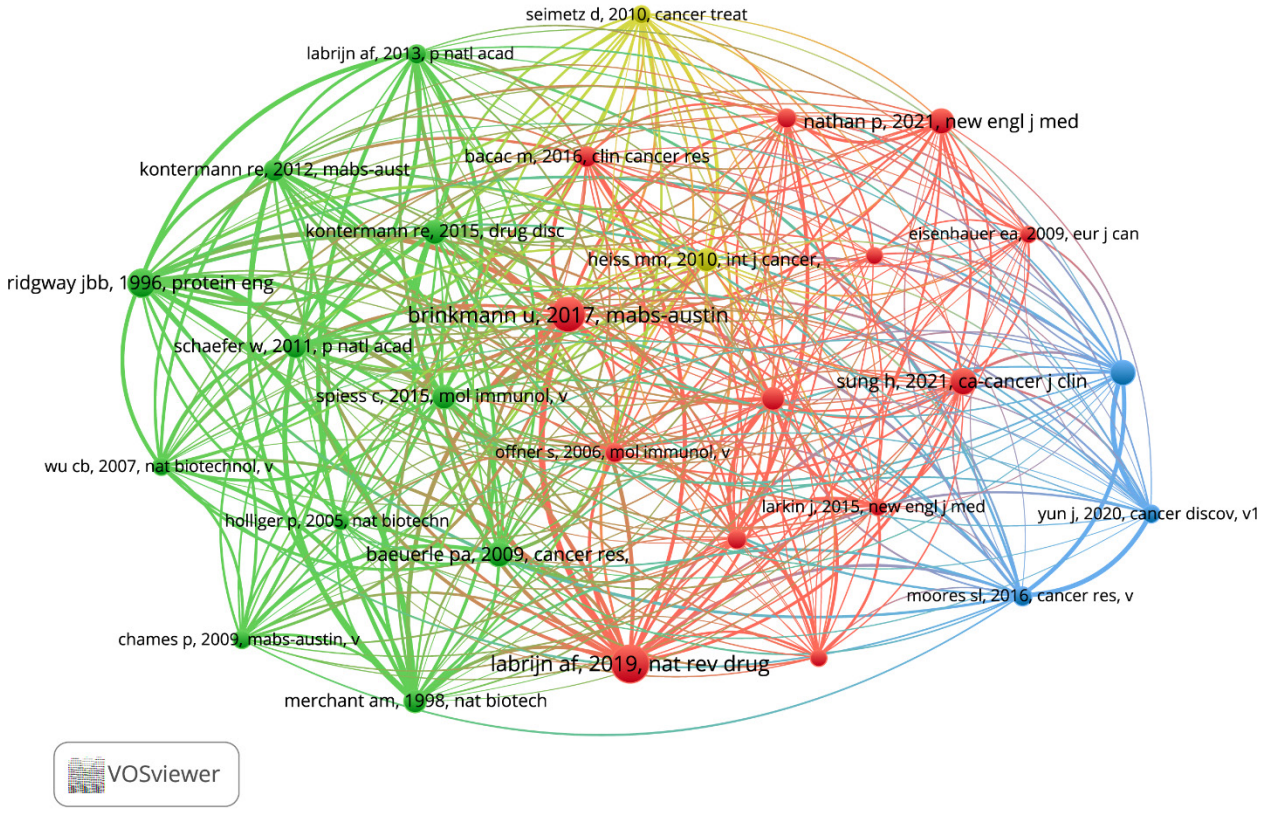

Figure 8. Visualization of co-cited references on bispecific antibody research in solid tumors.

3.6. References with citation bursts

The identification of the 25 references with the strongest citation bursts (**Figure 9**) highlights a selection of the most influential publications that achieved rapid and significant academic influence. The strongest citation bursts were associated with articles by Aran F Labrijn (2019, *Nat Rev Drug Discov*), Ulrich Brinkmann (2017, *MAbs*), and Christoph Spiess (2015, *Mol Immunol*). These three publications were all reviews that systematically summarized the research and development of BsAbs, with emphasis on structural design, production and clinical applications, respectively. More recently, studies by Paul Nathan (2021), Keunchil Park (2021), and Hyuna Sung (2021) have demonstrated vigorous citation bursts, underscoring the growing focus on pivotal clinical trials that led to the regulatory approval of BsAbs for solid tumors. These trials included tebentafusp for metastatic uveal melanoma and amivantamab for EGFR exon 20 insertion-

mutated non-small cell lung cancer (NSCLC).

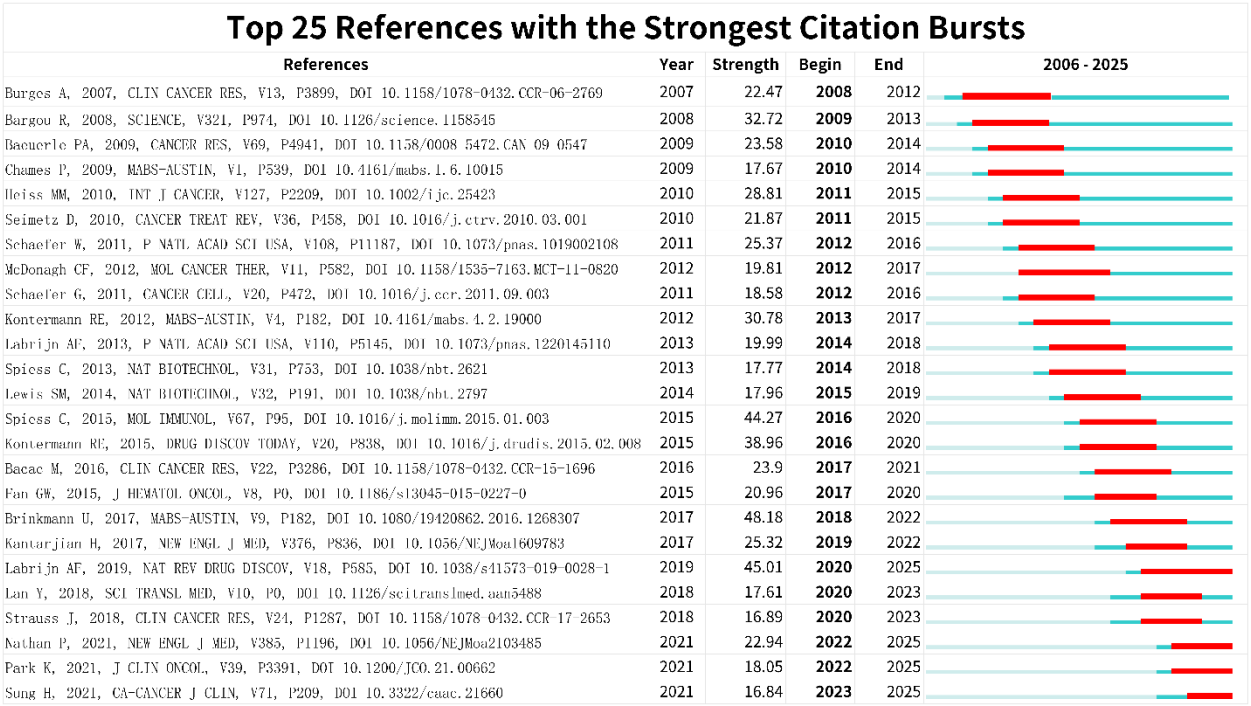

Figure 9. Top 25 references with the strongest citation bursts between 2006 and 2025.

3.7. Research hotspots and emerging trends

After the consolidation of synonymous terms, the 20 most frequently co-occurring keywords were obtained (**Table 5**). Major keywords included "BsAb" (n = 616), "immunotherapy" (n = 549) and "cancer" (n = 150), consistent with key topics of this field. It can be observed that "non-small cell lung cancer" stood out among keywords in terms of solid tumor types, suggesting an accelerated pace of BsAb research in this highly prevalent disease.

Table 5. Top 20 keywords on bispecific antibody research in solid tumors

Rank	Keywords	Counts	Rank	Keywords	Counts
1	Bispecific antibody	616	11	PD-L1	80
2	Immunotherapy	549	12	tumor microenvironment	78
3	Cancer	150	13	amivantamab	70
4	Cancer immunotherapy	143	14	immune checkpoint inhibitors	70
5	Non-small cell lung Cancer	117	15	bispecific	69
6	Targeted therapy	106	16	PD-1	63
7	Antibody	103	17	lung cancer	54
8	EGFR	103	18	antibody engineering	52
9	HER2	96	19	cd3	52
10	Breast cancer	87	20	monoclonal antibody	52

The analysis of keywords meeting the minimum occurrence threshold of 29 identified six main clusters (**Figure 10A**): The green cluster focuses on immunotherapy and tumor microenvironment (e.g., PD-1/

PD-L1 pathway), the red cluster centers on BsAbs (e.g., HER2/CD3-targeted agents), the blue cluster targets lung cancer therapy (specifically an anti-EGFR/c-MET [cellular-mesenchymal epithelial transition factor] BsAb for NSCLC), the purple cluster involves site-specific cancers (colorectal and prostate cancer), radioimmunotherapy with retargeting strategies, the cyan cluster centers on tebentafusp-mediated treatment for uveal melanoma, and the yellow cluster covers general targeted therapy and clinical trials. The hot spots represented by the core nodes (e.g., BsAb and immunotherapy) describe the major research themes for this field. Dense internal links and close nodes within clusters reflect the depth of studies on one theme, while cross-cluster links indicate synergistic integration between themes, which depicts a mature research ecosystem on target identification, drug development, and clinical translation.

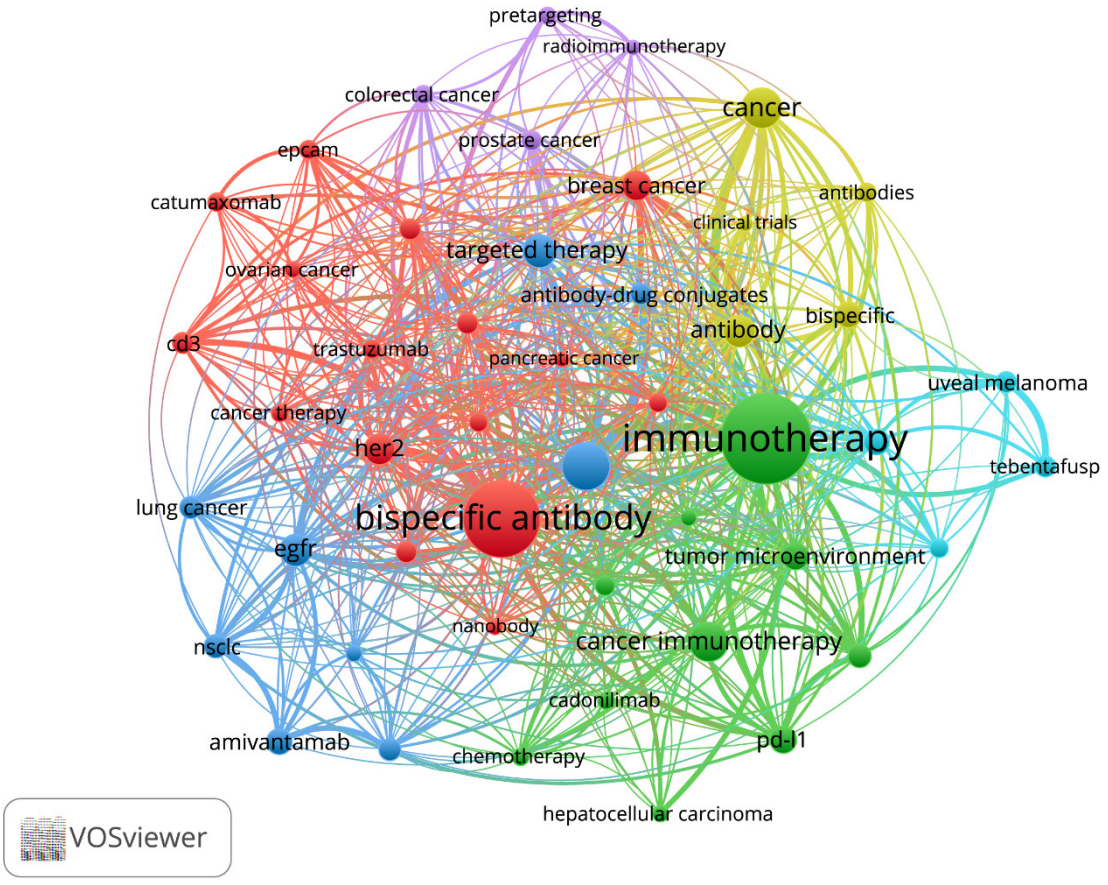

Figure 10A. Visualization of keywords with co-occurrence frequencies ≥ 29.

The top 25 keywords that exhibited the strongest citation bursts are shown in Figure 10B. A citation burst analysis revealed the emergence of keywords with a marked surge in citation frequency, as well as the duration of the citation bursts. The early bursts (2006–2010) identified the emergence of core antibody technology (monoclonal-antibody, strength = 27.17) and preclinical model (tumor-cells, ovarian cancer). The mid-stage (2011–2020) transitioned towards BsAb design and production technology (antibody engineering) and a specific BsAb (catumaxomab). The recent (2022–2025) bursts (open label, uveal melanoma) evidenced their clinical translation (trial design and clinical practice). Overall, it indicates the transition from basic

research to clinical translation, which steers BsAb therapy in solid tumors. The temporal evolution of keywords, as analyzed by trend topic analysis (**Figure 10C**), demonstrates a sustained upward trend in the frequency of BsAb-related terms from 2008 to 2024. This growth is matched with concurrent advances in immunotherapy and targeted therapy. The emergence of drug-specific topics (e.g., amivantamab and cadonilimab) reflects accelerated clinical translation. Overall, this trend indicates increasingly intensive BsAb research in solid tumors and rapid progression toward clinical application.

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2006 - 2025
monoclonal-antibody	2006	27.17	**2006**	2018	
accessory cells	2006	15.44	**2006**	2016	
fragments	2006	12.88	**2006**	2018	
in-vivo	2006	12.46	**2006**	2019	
carcinoma	2006	12.22	**2006**	2015	
single chain antibody	2006	11.03	**2006**	2014	
tumor-cells	2006	9.81	**2006**	2018	
single chain fv	2007	10.39	**2007**	2015	
biodistribution	2007	10.21	**2007**	2017	
in vivo	2007	9.87	**2007**	2018	
ovarian cancer	2007	8.4	**2007**	2013	
breast-cancer	2007	7.35	**2007**	2013	
malignant ascites	2008	25.24	**2008**	2016	
cancer-therapy	2008	17.42	**2008**	2018	
growth factor receptor	2007	15.63	**2009**	2017	
therapeutics	2010	7.85	**2010**	2018	
cancer therapy	2006	9.89	**2011**	2018	
monoclonal antibody	2006	9.42	**2011**	2017	
antibody engineering	2012	8.37	**2012**	2017	
catumaxomab	2012	8.2	**2012**	2016	
overexpression	2013	7.7	**2013**	2017	
trifunctional antibody catumaxomab	2014	8.6	**2014**	2016	
membrane antigen	2009	7.63	**2018**	2021	
open label	2020	14.87	**2022**	2025	
uveal melanoma	2022	8.01	**2022**	2025	

Figure 10B. Top 25 keywords with the strongest citation bursts between 2006 and 2025.

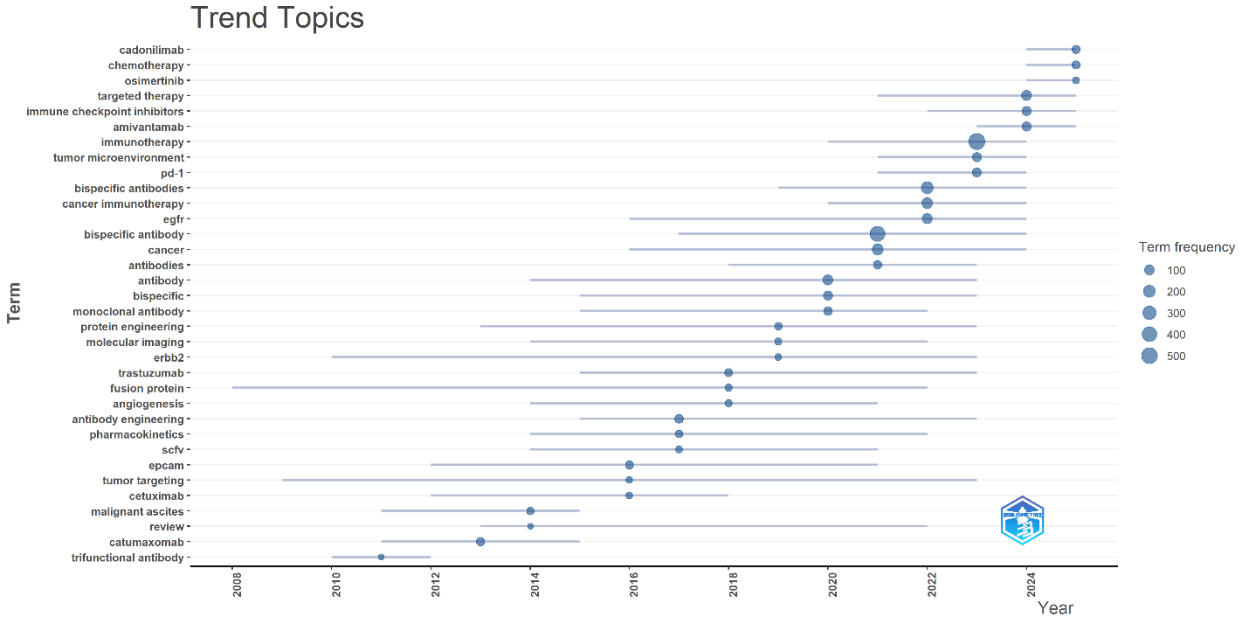

Figure 10C. Trend topic analysis on bispecific antibody research in solid tumors.

4. Discussion

BsAbs entered clinical trials in the 1990s [29]. With advances in genetic engineering technologies, the stability and immunogenicity of BsAbs have been substantially optimized. In 2014, blinatumomab received regulatory approval and marked the beginning of the bispecific T-cell engager (BiTE) era [15], laying the foundation for the rapid development of subsequent BsAbs. Compared with the huge success in hematologic malignancies, the use of BsAbs in solid tumors has developed relatively slowly. While catumaxomab was the first BsAb approved globally (for intraperitoneal therapy of malignant ascites), it was withdrawn for commercial reasons in 2017. Multiple approvals of BsAbs for solid tumors have only been seen in recent years. Four BsAbs were approved in 2024 for small cell lung cancer, NSCLC, biliary tract cancer and pancreatic cancer, respectively [2,17–19]. Currently, BsAbs have entered a phase of broad approval in China and the US, with numerous promising candidates advancing through phase III randomized controlled trials (RCTs) [10]. Therefore, the present bibliometric analysis was undertaken to provide a comprehensive overview of the research landscape, including its scale, pace of development, evolutionary trends and frontiers.

This study was conducted based on 3632 articles. The trend of yearly publications (**Figure 2**) showed that there was a significant rise in the number of relevant articles, with almost 60 % of total publications made in the last five years (2021–2025). This not only indicates the general scientific development trend, but is closely related to scientific breakthroughs of key technologies and clinical translation. A polynomial growth model ($R^2 = 0.9712$) strongly suggests that this expansion is systematic and sustained, driven by breakthroughs in antibody engineering, including robust platforms to ensure heavy-light chain pairing [30] and, as of recently, by the groundbreaking clinical approvals such as tebentafusp [25] and amivantamab [26]. This trend suggests that the field has reached an era of robust clinical trial validation and drug discovery from the experimental proof-of-concept phase.

Our analysis reveals a global research landscape characterized by pronounced geographic concentration and distinct national roles. The US and China together contributed nearly two-thirds of the publication

output. This could be due to several factors: substantial and sustained public and private funding for biomedical research, large patient populations allowing quick progress of clinical trials, and national policies that prioritize biopharmaceutical innovation [27,31]. In the global collaboration network (**Figure 3**), the US clearly acts as a core of the global biopharmaceutical industry with huge collaborations with other countries. In contrast, despite China's rise as an influential contributor in BsAb studies, its international connections seem to be weaker. A possible explanation is its large and self-sufficient domestic research environment [32], language and policy barriers, and the more recent integration of China's pharmaceutical innovation system into the global network [33].

At the institutional level, Memorial Sloan Kettering Cancer Center, National Cancer Institute, and Sun Yat-Sen University demonstrated the highest impact. The leadership of these academic medical centers indicates that the advancement of BsAbs in solid tumors is fundamentally a translational process dependent on the close integration of basic science, preclinical models, and early phase clinical trials [34]. The observed collaboration between academic institutions and pharmaceutical companies indicates a symbiotic model in which academic institutions drive target discovery and mechanistic understanding, while the industry provides the engineering scale, manufacturing expertise, and development capital required to commercialize complex biologic drugs. This type of academic-clinical-industrial triangle seems to be an important source of innovation in this domain [35].

Journal and co-citation analyses further elucidate the field's knowledge dissemination and validation pathways. The high productivity of journals such as *Front Immunol* and *MAbs* reflects the field's strong roots in immunology and antibody engineering [3]. In contrast, the most influential co-cited journals, such as *J Clin Oncol* and *N Engl J Med*, are high-impact platforms for clinical trial result reporting. This contrast illustrates a clear knowledge flow: foundational research published in specialized journals ultimately seeks validation in high-impact clinical publications. The co-citation clusters confirmed that fundamental mechanisms ("how BsAbs work"), clinical efficacy ("if they work in patients"), and specific drug applications ("where they work") are closely interconnected.

Our results on the co-authorship and the co-citation networks give complementary insights into the intellectual and collaboration architecture of the area. The co-authorship network revealed a fragmented landscape composed of tightly knit clusters with limited bridging between them, as seen in the relatively isolated cluster focused on tebentafusp. This indicates that, although research and cooperation seem to be strong in subfields, they could benefit from more collaboration across these subfields. On the contrary, we note a tightly interconnected knowledge basis from the co-citation network. Authors like Aran F. Labrijn and Roland E. Kontermann play the most central intellectual roles, and researchers in different subfields share the same basis of theory and methodology. The field's development process is grounded in a unified body of knowledge, and we speculate that it could be accelerated by strategic collaborations between subfields. Fostering such partnerships between distinct yet intellectually proximate groups could be the key to catalyzing future breakthroughs.

Co-cited references are publications cited together in other papers. An analysis of these references can demonstrate the connections between publications and help establish a field's knowledge base [36]. This analysis is therefore crucial for researchers to identify key achievements and evaluate the impact of specific studies in their fields. The top 10 co-cited references were predominantly landmark reviews or key clinical trials in the field of BsAbs. The most co-cited publication was the review by Labrijn et al. (2019) [22], which

provided a mechanistic classification of BsAbs and a summary of BsAbs' development process and current state, established an explicit classification and assessment framework. The review by Brinkmann et al. (2017) [12] categorized, analyzed, and comparatively discussed a variety of antibody formats in a systematic manner to give the theoretical basis and roadmap for research on BsAbs. Both works have made tremendous contributions to translating BsAbs from bench to bed. Ridgway et al. employed an "knobs-into-holes" (KiH) approach that achieved efficient and specific heterodimerization of antibody heavy chains, thereby laying a solid technological foundation for the subsequent development of BsAb platforms [28]. Merchant et al. combined KiH technology with an engineered disulfide bond and solved the issue of light-chain mispairing, resulting in a complete platform directly applicable to BsAb manufacturing. The combination of these two papers represents the technological foundations for current BsAb manufacturing. Tebentafusp, a first-in-class BiTE able to redirect T cells to gp100-expressing melanoma cells, has led to a strong overall survival benefit for uveal melanoma patients in a phase III RCT [25]. Amivantamab, a BsAb that simultaneously binds to EGFR and c-MET, demonstrated strong efficacy against EGFR exon 20 insertion mutations in the Chrysalis trial [4], resulting in its accelerated approval by the US Food and Drug Administration (FDA) for patients progressing on platinum-based chemotherapy. This established it as the first targeted therapy approved for this population in the US. Subsequent trials evaluating its use in the first-line setting for both EGFR exon 20 insertion mutations [37] and EGFR sensitizing mutations [38] have also reported positive outcomes, further supporting its clinical utility. Articles on the two clinical trials that led to the regulatory approval of tebentafusp and amivantamab were also ranked among the top 10 co-cited references. The growing involvement of researchers and the availability of established technology platforms are driving an increasing number of BsAbs in the clinical development of solid tumors. The presence of citation bursts in references is a key indicator of emerging research topics, as it reflects a sharp, recent increase in scholarly attention within a specific field [39]. As shown in **Figure 9**, the initial citation burst emerged from an article published in 2007 [40], which reported the phase I/II trial results of catumaxomab for malignant ascites in ovarian cancer and lasted until 2012. Citation bursts beginning around 2015 were mainly from review articles that discussed the design, formats, and early clinical investigations of BsAbs [8,41,42]. Meanwhile, the ongoing citation bursts associated with the literature on tebentafusp and amivantamab indicate their substantial academic and clinical impacts. Research frontiers shift from the design and production of BsAbs to their clinical use.

The keyword analysis provides important information on the focus and evolution of BsAb research in solid tumors. After removing general terms such as "BsAb" and "cancer," the predominant keywords identified include immunotherapy, targeted therapy, NSCLC, breast cancer, EGFR, and HER2 (**Table 5**). Based on their mechanisms of action, BsAbs in cancer therapy can be classified into two categories: the bridging type and the antigen cross-linking type [10]. Bridging-type BsAbs typically bind to antigens on both tumor cells and immune effector cells (e.g., T cells or natural killer cells), thereby activating effector cells to recognize and eliminate cancer cells [43]. In contrast, antigen cross-linking bsAbs simultaneously bind two distinct antigens or two different epitopes on a single antigen. This mechanism enables the effective co-inhibition of two disease-associated signaling pathways, such as immune checkpoint pathways (e.g., PD-1/CTLA-4) [44] or receptor tyrosine kinase pathways (e.g., EGFR and HER2) [44,45]. This likely accounts for the emergence of immunotherapy, targeted therapy, EGFR and HER2 as key terms in this field.

The keyword clustering provides a strategic framework for comprehending the disease-specific focus of BsAb research (**Figure 10A**). The clusters centered on NSCLC and HER2/CD3-targeted agents illustrate

a targeted research paradigm driven by major solid tumors. This pattern shows that research on BsAbs is progressing not as a pan-tumor agent, but rather focused towards specific oncological indications with huge unmet medical needs. The NSCLC cluster clearly indicates the rapid development of BsAbs directed against established tumor driver genes such as EGFR and c-MET [26], while the strong presence of HER2-directed BsAbs underscores their promising prospects in breast and gastric cancers [45,46]. This knowledge would be valuable for researchers and clinicians as it illustrates that the clinical achievement of BsAbs relies inherently on the choice of validated tumor antigens [47].

The temporal evolution of research focus, as revealed by citation burst strength and trend topic analysis, provides a compelling narrative of the field's maturation. The early bursts in "tumor-cells" and "in vivo" reflect the necessary preclinical groundwork, establishing the efficacy and mechanism of action of BsAbs in vitro and in animal models [48]. The subsequent shift towards "antibody engineering" signifies a phase of process optimization, addressing early challenges such as product stability and manufacturability [49]. The most recent bursts, highlighting "open label" trials and specific cancers like "uveal melanoma," mark the field's arrival at the clinical translation stage.

Overall, the keyword analysis illustrates a research community that has successfully passed its foundational and engineering phases and is now deeply engaged in the complex process of clinical application. The main implications for future research include facilitating the engineering of novel BsAb formats for specific medical needs, prioritizing combination approaches to overcome immunosuppressive TME, and learning from successful clinical translation drugs (such as amivantamab and tebentafusp) to inform clinical trial designs.

This work offers a systematic bibliometric landscape of BsAb research in solid tumors, covering immunotherapy and targeted therapy, which may provide valuable information. Multiple bibliometric tools, including CiteSpace, VOSviewer, and the R package "bibliometrix," were utilized to enhance the accuracy and depth of our analysis. However, this study had several limitations. Firstly, the literature search was conducted within a single database (WoSCC). Despite its comprehensive coverage of high-impact journals, WoSCC may omit relevant articles indexed exclusively in other databases, such as PubMed and Scopus. Secondly, the inclusion of only English-language publications could introduce language bias, as it might not fully capture the global research landscape. Finally, the citation-based impact of high-quality studies published in recent years is likely underestimated because of the citation delay effect.

5. Conclusion

The present bibliometric study outlined the dynamic development pattern of BsAb research in solid tumors during the last 20 years, indicating that this field has been garnering growing interest worldwide, especially in the US and China. This reference analysis reveals that BsAbs have successfully advanced from fundamental research to clinical application in the setting of solid tumors. However, the number of approved drugs remains limited. To accelerate future progress, it is imperative to enhance international collaboration and foster synergistic partnerships across distinct research subfields. The keyword evolution analysis demonstrates a clear trend from antibody engineering and preclinical research to the current focus on certain clinical applications, particularly in malignancies such as NSCLC and HER2-positive cancers. This shift highlights that the clinical success of BsAbs is intrinsically linked to targeting validated tumor-specific

antigens within well-defined patient populations. Future work should involve more rigorous clinical trials to expand the indications of BsAbs in solid tumors and to investigate their mechanisms of resistance and combination therapy strategies.

Disclosure statement

The authors declare no conflict of interest.

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