



## Research article

## The current status and future trends of BET research in oncology

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## ABSTRACT

**Background:** BET family proteins are important epigenetic and transcriptional regulators involved in the control of tumorigenesis and development and have become important targets for cancer therapy. However, there is no systematic bibliometric analysis in this field. A visual analysis of the research hotspots and trends of BET is helpful to understand the future development direction.

**Method:** We used CiteSpace, VOSviewer, and Excel to visualize and analyze the trends regarding authors, journals, countries or regions, highly cited papers, and keywords in the field.

**Result:** The results included a total of 946 publications. There are many more papers on BET proteins published since 2013. The papers are mainly from 44 countries, led by the U.S. and China. A total of 7381 authors were identified, among which Bradner, J.E. had the greatest number of articles and the greatest influence. Cancer Discovery was the journal with the most citations per article. Our analysis identified the most influential papers in the field, including highly cited papers and citation burst references. The most frequent keywords included 'expression', 'c-Myc', 'cancer', 'BRD4', 'BET inhibition', 'resistance', 'differentiation', and 'JQ1', which represent the focus of current and developing research fields.

**Conclusion:** Research on BET is thriving. Collaboration and exchanges between countries and institutions must be strengthened in the future, and the mechanisms of BET-related pathways, the relationship between BET and various diseases, and the development of new BET inhibitors have become the major focus of current research and the trend of future research.

## 1. Introduction

The bromodomain is a conserved 110-amino acid module, that includes the BET subfamily and is found in approximately 60 proteins in the human genome. The bromine domain is characterized by its four alpha helices (A, B, C, and Z), which are connected by two rings between the helices BC and ZA, and it is the only protein domain capable of binding to acetylated lysine residues. However, all four BET family members have an extraterminal (ET) domain, resulting in two N-terminal bromine domains in series (BDs, specifically BD1 and BD2) [1]. The proteins in the bromodomain and extraterminal (BET) family of proteins are important epigenetic and transcriptional regulator. They are highly important for normal cell growth and the cell cycle [2]. This discovery has caused researchers to consider whether BET inhibitors can be utilized for cancer therapy [3,4]. In view of the wide range of disease-related

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functions of BET, many BET inhibitors have been put into research [5]. JQ1 was the first reported pan-BET inhibitor, which was not put into clinical research due to its short half-life, but was widely used as a chemical probe to investigate the function and mechanism of effect of BRD4 and successfully used in preclinical proof-of-concept studies [6]. It has shown that BET proteins not only play a role in cancer progression, but also associated with metabolic disorders [7], HIV infection [8] and CNS disorders [9]. Recently, based on the concept of protein hydrolysis targeting chimera (PROTAC), heterobifunctional small molecule BET degraders have been designed to induce BET protein degradation. Zhou presented the design, synthesis and evaluation of a novel class of PROTAC BET degraders [10]. The BET family proteins include bromodomain-containing protein 2 (BRD2), BRD3, BRD4, and the testis-specific bromodomain-containing protein (BRDT) [11]. The BET family of proteins is powerful and plays an integral role in regulating gene expression [12]. BRD4 is a popular BET protein used in functional research. Currently, BET proteins, especially BRD4-targeted drugs, have proven their effectiveness in preclinical or clinical trials in lung cancer, breast cancer, leukemia, liver cancer, multiple myeloma, and other diseases [13]. Nevertheless, adverse events have been observed and may limit treatment adherence. Stathis reviews the preclinical rationale for targeting BET proteins in cancer and preliminary results from clinical trials, and outlines future directions for BET inhibitors as antitumor therapies [14]. Therefore, BET inhibitors are currently the focus field of research. The development of drugs targeting BRD4 is expected to bring new hope for the treatment of a variety of tumors.

Bibliometrics is a quantitative research tool that describes and analyses the dynamics and progress of a subject or a research field based on publication, citation, and text. Bibliometric analysis has become one of the most extensively used methods for assessing the credibility, quality, and reach of academic work [15,16]. Citation frequency is one of the measures used in the analysis [17]. as it refers to the number of times an article has been cited by researchers, articles with high citations can be said to have a greater impact on the scientific community. Bibliometrics, while not an absolute technique in itself, can be a valuable tool for guiding funding agencies in allocating resources and identifying potential research shortfalls in subject areas [18,19].

This paper analyses and summarizes the current research on BET proteins through bibliometric analysis, as well as a summary of existing issues and trends in BET protein research, in an effort to provide a more holistic outlook and analysis of the state of development of this field.

## 2. Data sources and research methods

### 2.1. Data sources

The data source used in this paper is the Web of Science Core Collection, because the Web of Science Core Collection has been accepted by many scholars as a high-quality digital literature resource database that is considered to be a relatively suitable database for bibliometric analysis [20]. Moreover, to ensure the comprehensiveness and accuracy of the retrieved data, the following indices were selected: SCI-EXPANDED and SSCI: TS= (BET OR bromodomain and extra-terminal) refined from 2013 to 01-01 to 2023-12-31 AND WEB OF SCIENCE CATEGORY (ONCOLOGY) AND DOCUMENT TYPES (ARTICLE OR REVIEW) AND LANGUAGES (ENGLISH). A total of 946 valid journal papers (798 articles and 148 reviews) were obtained after retrieval (Table 1). Firstly, we carried out data cleaning, for example, in the country analyses 'NORTH IRELAND', 'SCOTLAND', 'WALES', 'ENGLAND' were merged into 'UK'. In the keyword analysis, 'acquired resistance' and 'acquired-resistance' were merged. Details are attached in the supplementary material. To ensure the accuracy of the studies, two researchers conducted the searches while two others conducted the final checks, and those involved in the data retrieval and review worked independently.

### 2.2. Research methods

With the continuous development of big data and artificial intelligence technology, the trend in bibliometrics development is mainly reflected in its ability to utilize big data and artificial intelligence technology to mine and analyze the massive amounts of literature and information, and reveal its intrinsic regularity. Bibliometrics describes the laws between quantities and uses visual analysis to show the logical connections behind numbers. The study of the quantification of literature dates back to the early 20th century. In 1969, bibliologist Pritchard proposed to replaced documentary statistics with bibliometrics [21]. He extended the research object of documentary statistics from journals to all books and periodicals. Since then, bibliometrics has become an important branch of information science and philology [22]. During the analysis process, detailed information regarding authors, keywords, journals, countries, institutions, and references are available. Bibliometrics is based on several rules of empirical statistics. For example, Lotka's

**Table 1**  
Summary of data source and selection.

Category	Specific Standard Requirements
Research database	web of science core collection
Citation index	SCI-EXPANDED and SSCI
Searching period	January 2013 to December 2023
Language	English
Searching keywords	('BET' OR 'Bromodomain and extra-terminal')
Subject categories	'Oncology'
Document types	'Article or Review'
Sample size	946

law (1926) [23] represents the distribution of authors across scholarly publications; Zipf's Law provides the word frequency distribution in representative literature (1948) [24]; and Bradford's Law (1934) determines the distribution of papers in journals [25].

We used CiteSpace, VOSviewer, and Microsoft Excel for visual analysis. In this paper, the literature in the proposed research area is mapped and reviewed using CiteSpace and VOSviewer. VOSviewer is a program for constructing and viewing bibliometric maps [26, 27]. VOSviewer can construct and illustrate a bibliometric network map based on countries/regions, journals, authors, or keywords based on bibliographic, collaborative, citation, and cited data [26,28]. CiteSpace is a Java-based bibliometric software designed to help researchers discover the knowledge structure [29], research hotspots, tipping points, and future development trends in scientific fields [16]. CiteSpace can automatically extract keywords, authors, journals, institutions, and other information from the literature and use clustering, association, visualization, and other methods to present the information [30,31]. CiteSpace can analyze the citation relationship between studies and help users find important literature and research directions in the field of research [29]. CiteSpace can visually present the analysis results in the form of graphs and network diagrams to help users more intuitively understand the structure of knowledge and trends in the development of the field [32]. The two applications have their respective strengths and can be used together to complement each other.

### 3. Results

#### 3.1. Basic information

The 946 papers, 798 articles, and 178 reviews included in this study were authored by 7381 authors from 1532 institutions in 44 countries and were published in 148 journals; the citations included 37,873 articles (143 articles with citations>20) from 3156 journals (329 journals with citations>20).

#### 3.2. Quantity of publications

The chronological distribution of publications in the BET research area is shown in Fig. 1. Overall, research on BET in the field of oncology was at a nascent stage from 2003 to 2012 and began to grow rapidly in 2013, thus this paper selected the time span of 2013–2023 for the bibliometric analysis of the field of BET. To verify that the growth of publications on BET in oncology was consistent with Price's law, the collected data were put through an exponential and linear fit. The equation  $y = 1.9917e^{0.218x}$  (from its exponential curve a correlation coefficient of 0.5714 was obtained), and the other equation was linearly fitted  $y = 6.6325x - 25.1$  (correlation coefficient of 0.7987). The number of published articles in this area has shown an upward trend, especially since 2015; the number of publications has increased rapidly, indicating that BET proteins research has attracted increasing amounts of attention from scholars since 2016.

#### 3.3. Information on authors, journals, and countries

##### A Bibliometric analysis of authors

The representative scholars and core research forces of the research field can be identified through the analysis of authors in publications. Price, a famous scientist and historian of science, once stated as follows: 'that half of what is written on the same subject is written by productive authors, the number of which is approximately the square root of the total authors'. He once said that the total number of scientists grows roughly by the square of the number of outstanding scientist [21].

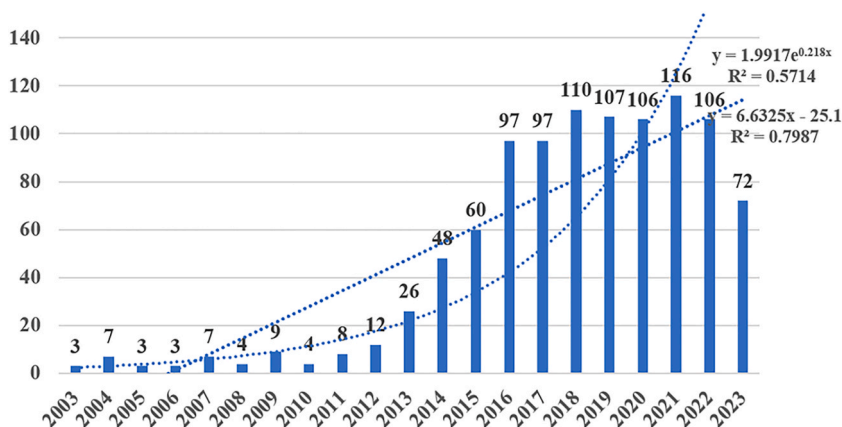


Fig. 1. The distribution of published papers from 2003 to 2023.

$$\sum_{m+1}^I n(x) = \sqrt{N}$$

In the above formula,  $n(x)$  represents the number of authors who have published  $x$  number of articles,  $I$  is the publication count for the most productive authors in the field (We can figure out  $I = 27$  from the VOSviewer statistics),  $N$  is the total number of authors, while  $m$  is the minimum number of publications by core authors.

$$m = 0.749 * \sqrt{I}$$

According to Price's law,  $m \sim 3.89$ . Therefore authors with more than 4 published papers were defined as the core authors in this field, and a total of 104 authors published 541 papers, accounting for 57.19 % of the total number of published papers, reaching half of the standard proposed by Price; therefore, we believe that a relatively stable group of authors has formed in BET research. The 10 most productive authors in this field are listed in Table 2. Among the highly productive authors, the most prolific is Bradner, J.E. In the past ten years, 27 articles by this author were published and cited 3214 times, with the average number of citations of each article reaching 119. Jun Qi, who is in second place, has a partnership with our laboratory and published a paper with us in *Biochimica et Biophysica Acta* entitled 'BET bromodomain is a novel regulator of TAZ and its activity' [33]. Qi has published 14 articles and has been cited a total of 2112 times, with each article cited 146 times on average. The aforementioned two authors worked together at Harvard University and have worked together many times. Based on the analysis of these publications, those two scientists have focused on the application of BET inhibitors as new drugs for diffuse large B-cell lymphoma [34], neuroblastoma [35], medulloblastoma [36], non-small cell lung cancer [37] and other diseases.

**B Bibliometric analysis of journals.** In regard to the distribution of literature in journals, we can often use Bradford's law as a demonstration. Bradford, a British chemist and documentarian, proposed this empirical law in 1948 as a quantitative description of the sequential structure of documents [38]. The specific content is expressed as follows: if the scientific journals are ranked by the number of papers published on a topic, in descending order, these journals can be classified into core areas and successive areas; then, the number of journals contained in the core area and that in the successive areas in a 1:  $a^2$  relationship ( $a > 1$ ).

In the field of BET research, we divided regions by the number of publications, as shown in Table 3. The number of publications in each of the three partitions is almost equal at this point, and the periodicals are approximately 1:4:16 (1:4:4<sup>2</sup>) in number, which is an indication that the distribution of publications in the field of BET research from 2013 to 2023 in journals basically complies with Bradford's law.

Subsequently, we calculated statistics on the journals to which the articles belonged. Table 4 shows the top 10 journals that have the highest average number of citations per article, most of which have an Impact Factor of more than 10.

### C Bibliometric analysis of counties

To better understand of which countries have made outstanding contributions to the field of BET research, this study analyzed the publication statuses of the 44 countries shown in Fig. 2. Next, we used VOSviewer to visualize the top 10 countries with more than 40 articles, as shown in Table 5. The U.S. was the country with the most articles published in the past decade, followed by China. It is worth noting that although the number of publications from France and the UK is relatively small, their average citations rank at the top. In addition, we obtained a visual map of cooperation between countries through the online analysis website of bibliometrics, the details of which are shown in Fig. 2. In Fig. 2A, the perimeter of each node indicates its number of documents and the scale of the outermost ring indicates its centrality. Fig. 2B shows a map of inter-country cooperation through the Bibliometrics Online Analysis website. Fig. 2C shows a map of cooperation between countries through VOSviewer.

### 3.4. Keywords

Words or terms selected from reports and papers for bibliographic indexing are named keywords, which are words that represent

**Table 2**  
The most important authors in the BET field.

Rank	Author	Documents	Citations	Average citation
1	Bradner, J.E.	27	3214	119.04
2	Qi, Jun	14	2112	150.86
3	Ocana, Alberto.	12	232	19.33
4	Pandiella, Atanasio.	11	222	20.18
5	French, Christopher A.	10	633	63.30
6	Knapp, Stefan.	10	630	63.00
7	Bhalla, Kapil N.	9	408	45.33
8	Stathis, Anastasios.	8	962	120.25
9	Bertoni, Francesco.	8	672	84.00
10	Cvitkovic, Esteban.	8	598	74.75

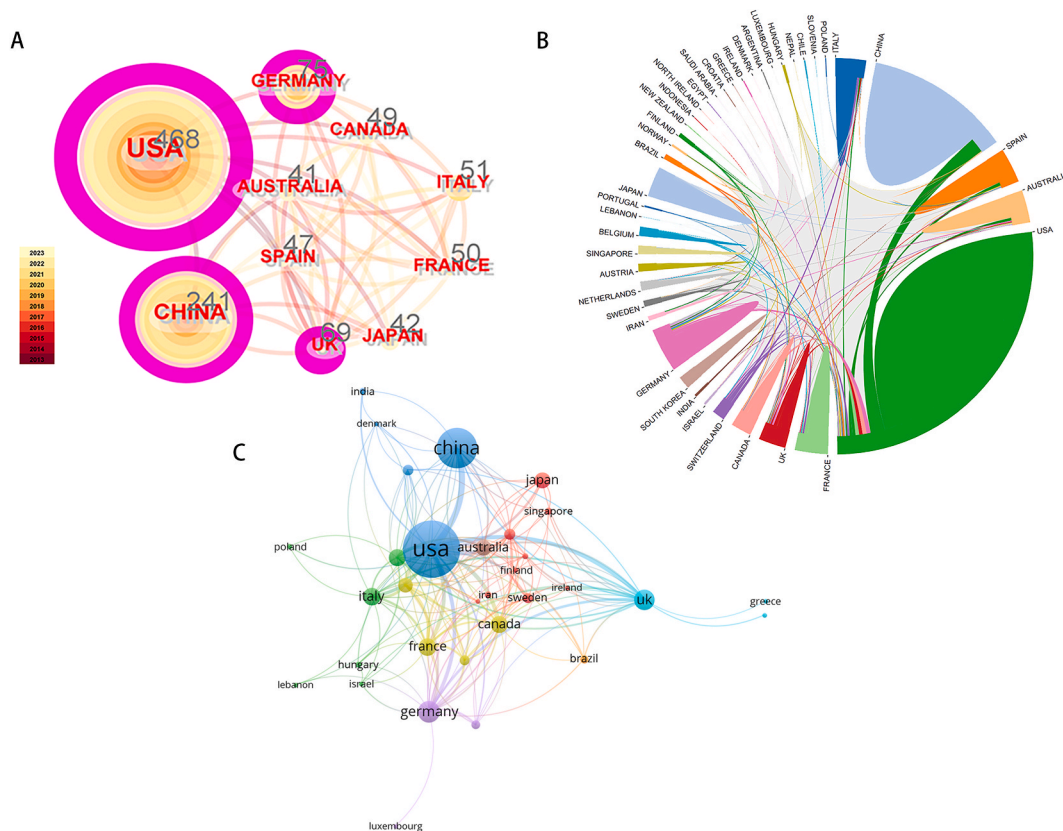
**Table 3**  
Journal partition.

Zone	Publication	Number of journals	Number of Publications
First Zone	≥35	6	317
Second Zone	7–34	29	360
Third Zone	1–6	113	269

**Table 4**  
Top ten most cited journals per article.

Rank	Source	Average Citation	Documents	2022JCI	2022IF/JCR
1	Cancer Discovery	137.31	16	5.89	29.1/Q1
2	Cancer Cell	134.38	16	6.44	50.3/Q1
3	Clinical Cancer Research	62.30	43	2.52	11.5/Q1
4	Cancer Immunology Research	59.86	14	2.07	10.1/Q1
5	Leukemia	51.31	54	1.99	11.4/Q1
6	Cancer Research	50.82	28	1.93	11.2/Q1
7	Oncogene	46.69	35	1.56	8.0/Q1
8	Oncotarget	39.41	74	a	5.168 <sup>a</sup>
9	Oncoimmunology	38.52	23	1.24	7.2/Q1
10	Molecular Cancer Therapeutics	36.58	50	1.16	5.7/Q2

<sup>a</sup> Data from IF-SCI-2016.



**Fig. 2.** Map of cooperation between countries. A. Co-occurrence of countries from CiteSpace. B. Map of cooperation between countries through the online analysis website of bibliometrics. C. Map of cooperation between countries from VOSviewer.

the core and essence of the paper and are used to indicate information about the subject in the full text. In addition, keywords co-occurrence analysis sheds light on the hot topics of research in a particular scientific field. To obtain more detailed information on the keywords, VOSviewer was used to construct a keyword co-occurrence network view of 946 pieces of literature, and the top 98 keywords with a frequency greater than 17 were selected for visualization analysis, as shown in Fig. 3. The larger the circle node in the

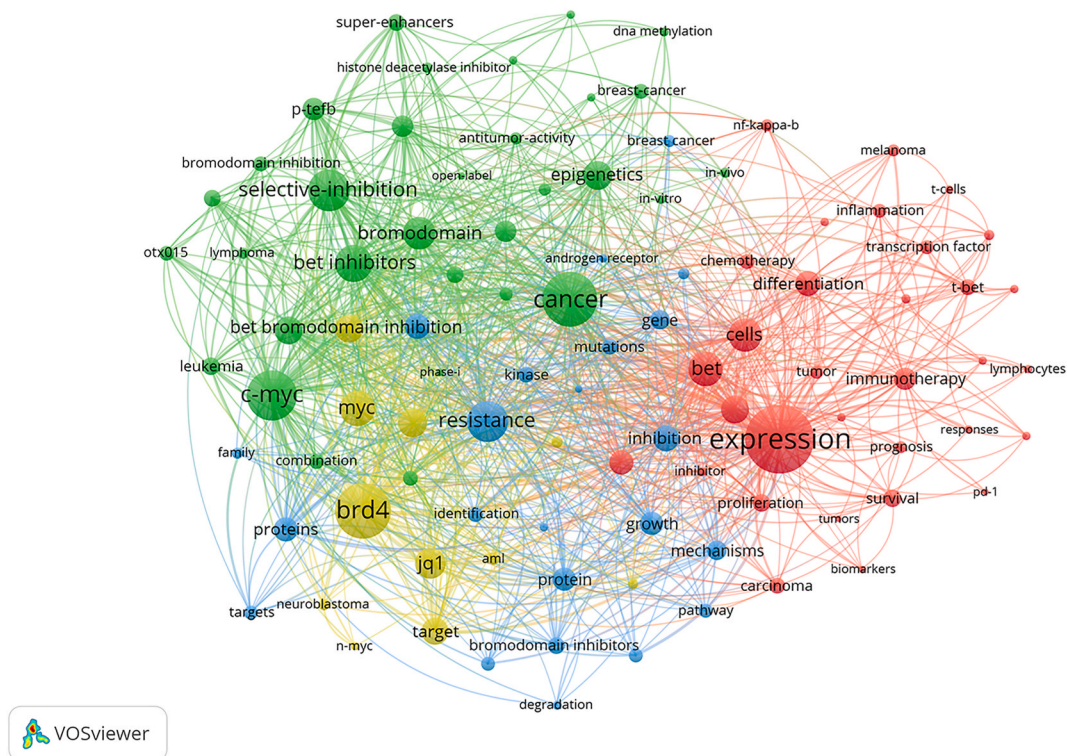
**Table 5**  
Top 10 countries in BET field.

Rank	Country	Documents	Citations	Average Citation
1	USA	436	20168	46.26
2	China	218	5767	26.45
3	Germany	71	1880	26.48
4	UK	57	3892	68.28
5	Italy	50	2259	45.18
6	France	49	3316	67.67
7	Canada	47	2059	43.81
8	Spain	45	1748	38.84
9	Japan	40	1102	27.55
10	Australia	39	1391	35.67

figure is, the more frequently the keywords appears, the more it can represent the hot spot in the field, and the size of the node connection represents the correlation intensity. The thicker the line is, the more likely the two appear together in a paper, and the node color represents different clusters (research topics).

Moreover, high-frequency keywords are those keywords used more than 11 times (according to Price's theorem), as shown in Fig. 4. As shown in the figure 'expression', 'c-Myc', 'cancer', 'BRD4', 'BET-inhibition', 'resistance', 'differentiation', and 'JQ1' are the representative terms used in this field. In addition, we sorted the keywords to obtain the top critical molecules, phenotypes, diseases, and cell types mentioned in BET studies, as shown in Table 6. The most common key molecules are c-Myc, BRD4, p-TEFb, and NF-kappa-B, and the most common disease occurrences in BET studies include AML, breast-cancer, colorectal-cancer, leukemia, and lung cancer. The phenotypes that appeared the most often in BET studies were differentiation, apoptosis, proliferation, progression, and metastasis. The cells that seemed the most common in BET studies were stem-cells, regulatory T-cells, T-cells, dendritic cells, and lymphocytes.

To provide an overview of the progress of the temporal dimension in the BET research field, the keyword co-occurrence network map shown in Fig. 5 was generated using the timeline map provided by CiteSpace to show the periodic changes in these research hotspots in recent years. Fig. 5 shows that the retrieved literature can be divided into eleven clusters and the research hotspots of each period are presented on the corresponding timeline of each cluster. According to the clustering results, cluster #8 and #9 appeared more recently than cluster #10. Early research focused on chronic disease, randomized controlled trial and c-Myc, while recent research has focused on endothelial-to-mesenchymal transition, small-cell-lung cancer, and liver immune system.



**Fig. 3.** Map of co-occurrence keywords.

CiteSpace, v. 6.2.R4 (64-bit) Advanced  
 January 26, 2024 at 8:24:32 PM CST  
 WoS: C:\Users\1\Desktop\bet\cite\_spacedata  
 Timespan: 2013-2023 (Slice Length=1)  
 Selection Criteria: g-index (k=25), LRF=3.0, LN=10, LB=5, e=1.0  
 Network: N=375, E=2979 (Density=0.0425)  
 Largest CCs: 375 (100%)  
 Nodes Labeled: 1.0%  
 Pruning: None

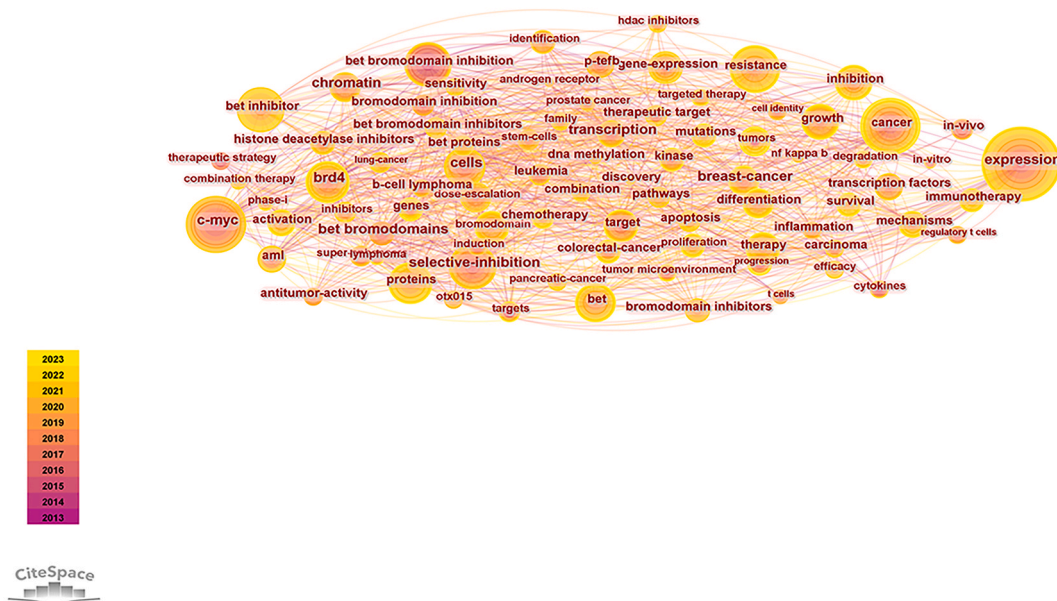


Fig. 4. Map of high-frequency keywords.

Table 6  
 Top 5 key molecules, states, diseases, and cell types in a study on BET.

Rank	Molecule	Occurrence	State	Occurrence	Disease	Occurrence	Cell	Occurrence
1	c-Myc	163	differentiation	72	AML	67	stem-cells	22
2	BRD4	96	apoptosis	44	breast-cancer	65	regulatory t-cells	17
3	p-TEFb	47	proliferation	30	colorectal-cancer	33	t-cells	12
4	NF-kappa-B	20	progression	20	leukemia	31	dendritic cells	16
5	IFN-gamma	11	metastasis	11	lung cancer	16	lymphocytes	15

To obtain a clearer understanding of burst analysis in the field of BET research, the burst analysis function of CiteSpace was further applied. The results of the analysis are shown in Fig. 6. Burst words, to some extent, can reveal a new phenomenon in the field of science. This information can not only reveal the evolution of hot topics in the research field over time but also reveal the research trends in recent years to provide a reference for the future. The strongest citation bursts mean that the variation of the variable changed a lot in a short period of time. The red bar indicates the duration of the bursts. The greatest burst length was 12.28 for BTE bromodomain inhibition, which started in 2013 and ended in 2016. Immunotherapy, BET inhibitor and lung-cancer emerged in 2015, revealing prominent research trends in the field of oncology.

### 3.5. Citation

The top 10 articles with the highest total citations are listed in Table 7. The highest ranked article was ‘Discovery and Characterization of Super-Enhancer-Associated Dependencies in Diffuse Large B-Cell Lymphoma’ in 2013 by Chapuy, B., which was published in *Cancer Cell* and was cited 549 times in total. This article implies that BET inhibitors selectively target oncogenic and lineage-specific transcriptional circuits in diffuse large B-cell lymphoma (DLBCL) and suggests strategies for uncovering unrecognized cancer dependencies, establishing a basis for evaluating the therapeutic basis of BET inhibitors in this disease [34].

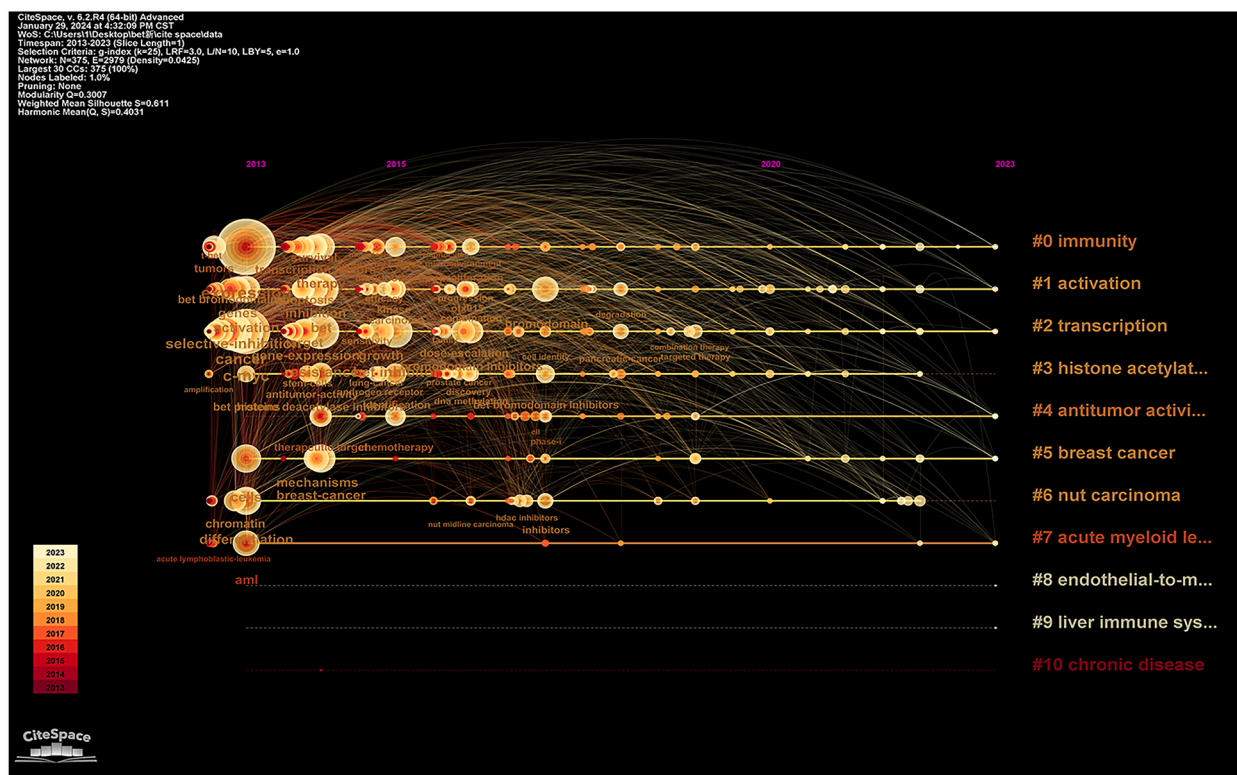


Fig. 5. Map of timeline view.

### 3.6. Co-citation

Co-citation analysis aims to grasp the most frequently cited papers and journals in the research field. We created the journal co-citation map using VOSviewer, setting the threshold to a minimum of 150 citations of a journal; 61 journals remained for use in the co-citation analysis. The results are presented in Fig. 7. Fig. 7 shows that the co-citation network of journals consists of five clusters. Among the five clusters, the blue cluster was associated mainly with immunology journals, and the green cluster was associated mainly with life science journals, focusing on the use of BET proteins in cytology, molecular biology, and genetics research. These periodicals were cited to analyze the existing research and to provide theoretical and empirical support for their own research. The red, purple, and yellow clustered journals focused primarily on clinical diseases and drugs and tended to include more research on clinical drug treatment. These periodicals were cited mainly to provide technical support for the research.

Then, we used VOSviewer to construct a co-citation map of the references, with the minimum threshold of co-citations set to 46, leaving 35 studies for co-citation analysis of the cited papers; the final result shown in Fig. 8. An analysis of the publication years of high co-citation papers showed that high co-citation papers were mainly concentrated between 2011 and 2013, and the number of times that the studies published in the last five years were cited was less than those published from 2011 to 2013.

## 4. Discussion

In bibliometrics, CiteSpace, developed by Professor Chao-Mei Chen, stands out as an essential tool that utilizes Java for conducting comprehensive co-citation network analyses. This software excels in revealing significant trends and changes in scientific research, mapping the progress of various research fields, and highlighting emerging studies [39,40]. It effectively illuminates the growing importance and integration of ecosystem services research from 1981 to 2017 within the global scientific community [41]. Furthermore, Ahmad and Slots' bibliometric analysis in 'Periodontology 2000' helps delineate major research trends and significant works in periodontology, enhancing our understanding of the field's evolution and current focus areas [42].

### 4.1. General information

The 946 papers included in this study were authored by 7381 authors from 1532 institutions in 44 countries and were published in 148 journals.

Over the period included in this study, the number of BET studies in oncology has generally shown a gradual increase, and there is still much to develop in the future. First, there are still many problems in oncology that need to be explored, such as the pathogenesis of



## Top 20 Keywords with the Strongest Citation Bursts

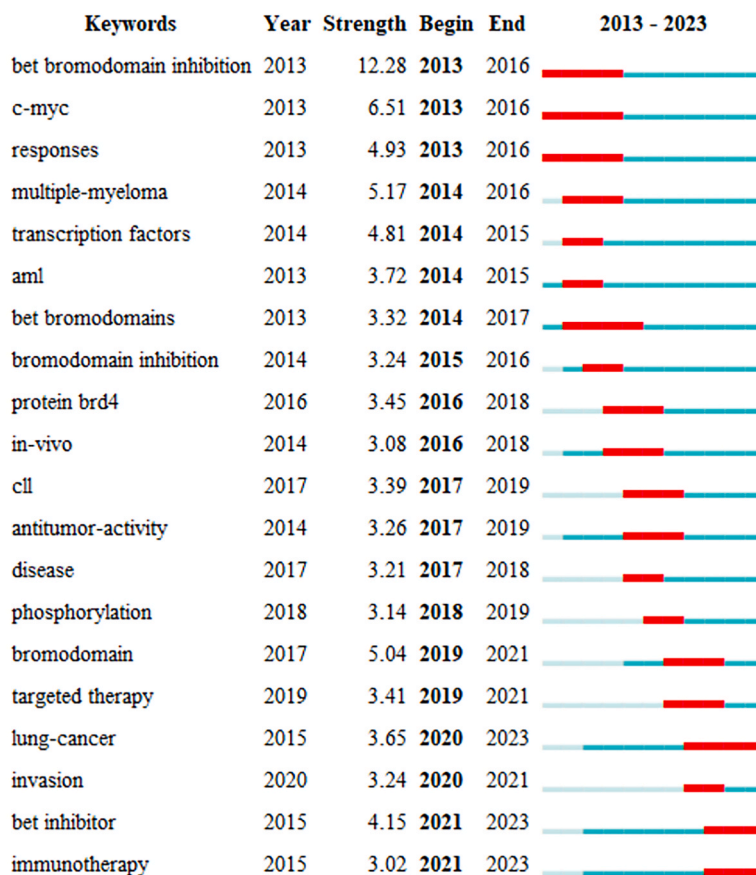


Fig. 6. Burst analysis of top 20 keywords in BET.

Table 7

Top 10 highly cited documents on BET in oncology.

Rank	Publication year	Title	First author	citations
1	2013	Discovery and Characterization of Super-Enhancer-Associated Dependencies in Diffuse Large B Cell Lymphoma	Chapuy, B.	549
2	2013	Targeting MYCN in Neuroblastoma by BET Bromodomain Inhibition	Puissant, A.	478
3	2018	BRD4 and Cancer: going beyond transcriptional regulation	Donati, Benedetta	346
4	2018	BET Proteins as Targets for Anticancer Treatment	Stathis, Anastasios	288
5	2015	Genomic alterations in lung adenocarcinoma	Devarakonda, Siddhartha	284
6	2017	Differentiation therapy revisited	de The, Hugues	269
7	2014	BET Bromodomain Inhibition of MYC-Amplified Medulloblastoma	Bandopadhyay, Pratiti	254
8	2016	Clinical Response of Carcinomas Harboring the BRD4-NUT Oncoprotein to the Targeted Bromodomain Inhibitor OTX015/MK-8628	Stathis, Anastasios	252
9	2013	Inhibition of BET Bromodomain Targets Genetically Diverse Glioblastoma	Cheng, Zhixiang	238
10	2017	<a href="#">BET inhibitors: a novel epigenetic approach</a>	Doroshov, D. B.	230

key molecules, the influence of signaling pathways on the occurrence and development of cancer, the development of new antitumor drugs, and the problem of drug resistance. Such research may continue to be the focus of future research. In addition, with the development of the economy and the improvement of standards of living, people are not only paying attention to food and clothing but also paying more attention to medical health. According to the latest global cancer burden estimates from the International Agency for Research on Cancer, there will be an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths worldwide in 2020. Cancer is the leading cause of death and a major obstacle to increasing life expectancy in countries around the world [43,44].

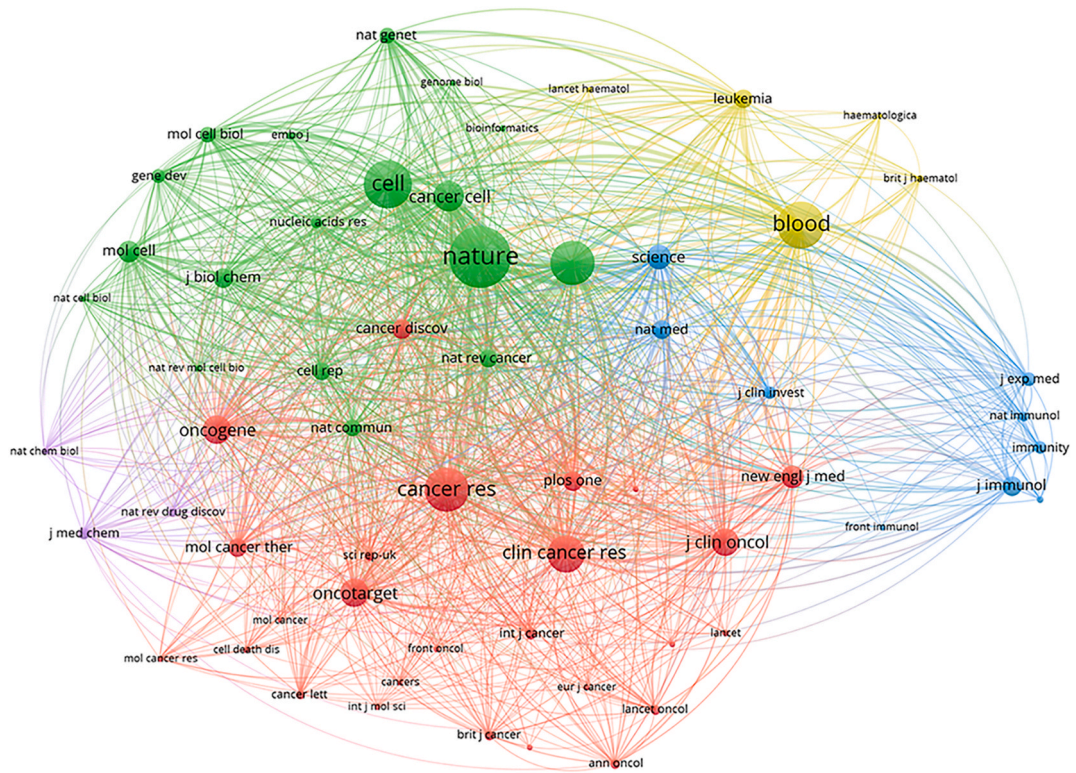


Fig. 7. Map of co-citation network of journals.

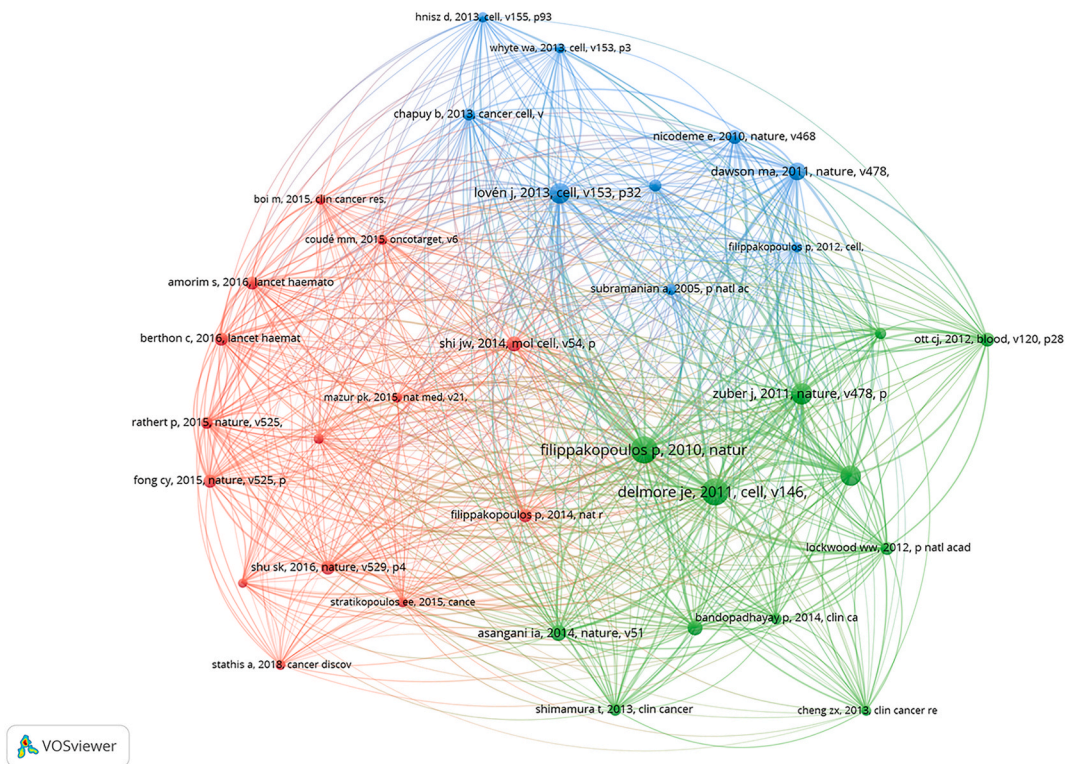


Fig. 8. Map of co-citation references.



The field of BET research crosses the disciplines of oncology, pharmacy, and immunology and has received much attention at present; thus, BET protein research is a topic worthy of continuous iterative updating. One of the reasons for choosing this topic is that we have focused on the field of antitumor drugs, and we have cooperated with Qi, the second-highest-ranking author in terms of volume of papers published in this field in the last decade. On the other hand, my own project is related to the molecular mechanism of BET inhibitors in colorectal cancer. The research subjects of bibliometrics are mainly literature and information, including the quantity, structure, distribution and citation relationships. Through the study of these aspects, bibliometrics can reveal the internal regularity of the literature and related information, thus providing important references and guidance for scholars in the tumor disciplines under study. In our study, VOSviewer and CiteSpace software were used to analyze the related research in this field in the past decade, systematically review the potential trends in this field, and validate of Price's Law and Bradford's Law in this area. The core authors, high-productivity countries, journals, and keyword clusters in this area are discussed and analyzed. The conclusions obtained based on the quantitative analysis are summarized as follows.

The annual publication volume data (Fig. 1) showed that the annual publication volume in the BET field generally increased over the past decade, especially after 2015. With adjustment into tendency lines, the growth pattern of the obtained publications tends to fit a linear equation rather than an exponential trend according to its linear equation  $y = 6.6325x - 25.1$  with a correlation coefficient of 0.7987 points to a strong positive relationship between time and publication volume, affirming the consistent growth in this field. The severity of the 2022 epidemic in the country, which led to government measures restricting the movement of people and goods, may have had a severe impact on the transport and delivery of reagents. Under these conditions, many laboratories are experiencing reagent shortages, and experimental progress is being hampered. Reagents are an essential part of scientific research, and help researchers perform complex analytical and experimental procedures. However, as a result of the outbreak, the reagent supply chain has been severely disrupted and reagent prices have risen dramatically. These problems not only caused major difficulties in scientific research but also had a negative impact on the investigation and treatment of the outbreak.

#### 4.2. Hotspots and frontiers

In addition, in the early years, the focus of the BET field was mainly on the involvement of the BET inhibitor JQ1 in regulating Myc to suppress hematological diseases, and the literature published in 2022 focused on the association of BET inhibitors with immune escape mechanisms [45,46] and the development of new BET inhibitors [47]. These studies not only broaden our understanding of BET inhibitors in the context of cancer biology, but also highlight potential new therapeutic pathways. In addition, the regulatory role of BRD4 in tumors is related to post-translational modification; therefore, targeting BRD4-related modification sites may be an effective strategy for cancer prevention and treatment [48]. This advancement underscores the importance of post-translational modifications in oncology, paving the way for novel intervention strategies. This indicates that the research in the field of BET has become deeper and broader in recent years, providing the impetus for the development of new BET inhibitors and providing new hope for the treatment of tumors. In addition, in the early years, the main diseases under investigation were hematological tumors and nonsolid tumors. In 2022, more solid tumors and other highly malignant tumors appeared, signifying a shift in research focus that could lead to more inclusive and comprehensive cancer therapies. This indicate that with the support of long-term research and development of new BET inhibitors, BET inhibitors are expected to be used as a treatment or combination therapy for a variety of hematological and solid tumors, becoming pan-cancer inhibitors. This expansion of the therapeutic scope suggests that BET inhibitors have the potential to transform cancer treatment across a broad spectrum of tumor types.

In the field of BET research, a consistent and established group of contributors has formed, with several notable scholars making significant impacts. The most prolific author was Bradner J.E., with 27 articles published in the last decade and 3214 citations, with the average citation times of each article reaching 119.04 times highlighting the substantial influence and recognition of his work within the scientific community. Qi, who is in second place, published 14 articles and was cited 2112 times in total, with an average of 150.86 times per article, demonstrating high engagement with his research outputs. According to the analysis of the results, productive researchers tend to collaborate and communicate, which enhance their research impact and visibility. The authors mentioned above, both of whom work at Harvard University, have collaborated several times. This pattern underscores the importance of academic partnerships in advancing research and enhancing the scholarly impact. It is worth mentioning that our university also has a collaborative network in the BET research area. CSU published a total of 14 papers, most of which were published in 2021 and 2022, indicating that CSU has recently invested more research in and attention to the field of BET. In terms of international collaboration, CSU published a paper with Emory University on the novel biological function of BET inhibitors in regulating apoptosis [49], which was published in 2015 and has been cited 33 times, and on the ability of BET inhibitors to restore the development of acquired resistance to osimertinib [50], which was published in 2021 with 13 citations. In addition, CSU has cooperated with the University of Pittsburgh on the use of BET inhibitors to enhance the effect of chemotherapy in colorectal cancer by inducing DR5 [51], demonstrating the efficacy of BET inhibitors alone and in combination with chemotherapy in treating colorectal cancer. In terms of domestic collaboration, collaborations between CSU and Nanchang University have led to the finding that BET inhibitors attenuate renal fibrosis and block epithelial mesenchymal transition (EMT) by altering the expression of EMT-related proteins [52]. These results highlight the global cooperative efforts that enrich the research landscape and contribute to the broader understanding of BET inhibitors' therapeutic potential. A collaboration among CSU, Bengbu Medical College, and Shanghai Jiao Tong University revealed the critical function of BET inhibitors in ARID1A-deficient lung tumors and their potential as drug targets [53]. As shown in the study by CSU and Shanghai Jiao Tong University, the novel and highly potent BET inhibitor NHWD-870 [54], developed by Professor Mingzhu Yin's group at Xiangya Hospital, Central South University, may lead to inhibition of the STAT3 signal and thereby interfere with osteosarcoma progression. In addition, the ability of NHWD-870 to interfere with the vicious cycle of tumor progression and bone

destruction may be a promising therapeutic strategy for bone-related tumors [55]. BET inhibitors disrupt the binding of BET proteins to acetylated lysine residues in chromatin and inhibit the transcription of several genes, including oncogenic transcription factors, providing a new approach to epigenomic and transcriptomic cancer therapy. Overall, these collaborations and individual achievements not only advance the scientific understanding of BET inhibitors but also illustrate the critical role of academic networks in fostering innovation and translating research into practical applications.

The imbalance of research development in different countries or regions may be related to the level of the economy, culture, scientific and technological development, geographical climate, resource conditions, and the degree of attention given to medicine. In the past decade, the U.S. and China had the largest number of publications and the highest total number of citations (Fig. 2, Table 5); however, although UK and France ranked fourth and fifth in terms of publications, respectively, the average number of citations of each country was greater than those of the U.S. and China. This suggests that while the quantity of research output in UK and France may be lower, the quality, as indicated by citation metrics, is comparatively higher. Researchers in China and the U.S. performed more research in the BET field, while researchers in UK and France have more influence in the BET field. This pattern reflects a strategic focus on niche areas within the BET field in England UK and France, potentially driven by specific funding priorities, research agendas, and academic collaborations that emphasize impactful research over sheer volume.

The main journals that published papers in this field were Life Science, Immunology, and Pharmacy. According to the results of this study, most of the journals with a large number of papers in the BET field belong to JCR Q1 (Table 4), indicating that the predecessors have laid a good foundation for BET research. This high concentration in top-tier journals suggests that BET research is both impactful and recognized within the scientific community. On May 20, 2021, a new index named the Journal Citation Indicator (JCI) was added to the 2021 edition of the Journal Citation Report (JCR), which was entered into the WoS database for use. The JCI is the impact index (CNCI) of all articles (including reviews) published in a journal in the past three years. In practical calculations, a value of 1.0 is the baseline for measuring journal citation performance. A journal citation index above 1.0 indicates that the journal exceeds the average citation level. This signifies that journals with a JCI greater than 1.0 are contributing more significantly to their fields compared to their peers, enhancing the dissemination and impact of research conducted in these areas. All of the top 10 journals have a higher citation impact than the average for their category.

#### 4.3. Role of BET in disease

Co-occurrence analysis and evolution analysis of keywords revealed that the research field has developed rapidly in the last decade, the breadth and depth of this field have greatly expanded, and the use of technology has become more profound. Researchers are also concerned about ethical issues in the process of data collection and application. The most common key molecules mentioned are c-Myc, BRD4, p-TEFb, and NF-kappa-B, and the most common diseases mentioned in studies on BET include AML, breast-cancer, colorectal-cancer, leukemia and lung cancer. These findings reflect a clear focus on translational research aimed at bridging the gap between basic science and therapeutic applications. The phenotypes that appeared most often in BET studies were differentiation, apoptosis, proliferation, progression, and metastasis. In addition, selective inhibitors and drug resistance are also hot keywords in this field, which indicates that bet is closely related to treatment in the field of cancer, and researchers have made efforts to develop new drugs that provide new ideas for the treatment of cancer. The mention of selective inhibitors and drug resistance highlights a pivotal area of concern in the ongoing battle against cancer, emphasizing the urgent need for novel therapeutic strategies that can overcome these challenges. Immunotherapy and lung cancer have been prominent research trends in the field of oncology since 2015, which signifies these areas as pivotal axes in oncology research, pointing to them as critical frontiers in improving cancer treatment outcomes.

According to the analysis of highly cited literature, BET inhibitors inhibit neuroblastoma growth *in vivo* by regulating n-Myc transcription [35], inhibit Myc expression in medulloblastoma [36], resulting in an overall reduction in medulloblastoma cell viability, and modulate Myc activity to inhibit NUT midline carcinoma (NMC) development. Moreover, BET inhibitors significantly repress the growth of orthotopic glioblastoma tumors [56]. These observations suggest that BET inhibitors target molecular pathways critical for tumor growth and viability across various cancer types. These findings indicate that BET inhibitors have certain inhibitory effects on a variety of hematological tumors and solid tumors. This broad spectrum of action underscores their potential as versatile, multi-cancer therapeutics. Therefore, new BET inhibitors are expected to be developed for use as a pan-cancer drug and provide new ideas for clinical treatment.

The co-citation analysis revealed the most cited journals and literature in the field, facilitating subsequent scholars in exploring the core research in this field and making it easier for later scholars to grasp the core content and overall framework of this field faster. The co-cited references were mainly from journals in the fields of immunology, life sciences, clinical diseases, and pharmaceuticals; they focused on BET applications in cytology, molecular biology, and genetics and provided new ideas for the development of new clinical drugs and combination therapy. This indicates a strong, interdisciplinary interest in BET's role within these vital areas of research. By highlighting these key areas, the analysis not only maps out the intellectual landscape but also points to potential fruitful areas for future investigation. These insights could accelerate the development of novel therapeutic strategies and enhance the understanding of the underlying mechanisms at play in various diseases.

#### 4.4. Limitations

Due to the influence of several objective factors, this study has certain limitations. First, to ensure the quality and integrity of the collected data, bibliometric analysis software has high norms and standards for data; this study selected papers in only the two indexes of the SSCI and SCIE in the core collection of the Web of Science database, excluding other databases. This approach will inevitably

lead to the problem that the analysis data are not comprehensive enough. However, WoS is the most commonly used database for scientific metrological analyses, and WoS has been accepted by many researchers as a high-quality database of digital literature resources. In addition, deeper and more comprehensive research is needed in this area, as quantitative analysis requires the analysis and interpretation of data. Otherwise, there will inevitably be a certain degree of subjectivity.

## 5. Conclusion and Prospect

This study provides the first bibliometric cluster analysis and visualization of BET research in the field of oncology. This extensive bibliometric analysis provides a comprehensive overview of the BET research field from 2013 to 2023. Papers on BET research generally show a growing trend. Globally, the United States and China are the leading countries conducting this research. *Cancer Discovery* and *Cancer Cell* are two of the more influential journals in the field of oncology for BET research. Bradner, J.E. is the most prominent contributor to BET research. There is a need for greater collaboration and exchange between different countries, institutions, and authors to accomplish high-level studies. Currently, the research on BET proteins has focused on drug discovery, drug-targeted therapy, and drug-combination therapy. In summary, this study provides a visualization of current research findings and future research trends in this field through data analysis of existing studies.

There are reasons to believe that BET research will continuously and dynamically continue to develop, which is of further significance and value. In future research, it will be necessary to integrate papers from multiple databases to ensure the comprehensiveness of the data and actively contact BET researchers to gain a better understanding of the frontier dynamics of this field, enhance and deepen the objective cognition of the area, and avoid, as far as possible, the subjectivity of individual analysis and interpretation.

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## Data availability statement

Data will be made available on request.

## CRediT authorship contribution statement

**Siying Yu:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Linna Long:** Visualization, Investigation, Formal analysis. **Xiaorui Zhang:** Methodology, Formal analysis. **Yu Qiu:** Visualization, Investigation. **Yabo Huang:** Investigation. **Xueying Huang:** Visualization, Methodology, Investigation. **Xia Li:** Visualization, Investigation. **Rong Xu:** Investigation. **Chunmei Fan:** Validation, Supervision, Software, Investigation, Funding acquisition. **He Huang:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing interest

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

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e36888>.

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