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Research hotspots and frontier analysis of the novel immune checkpoint Nectin-4

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ABSTRACT

Nectin-4 has emerged as a pivotal therapeutic target for antibody-drug conjugates (ADCs), particularly in advanced urothelial carcinoma (aUC) research. Although extensive literature has been reported on Nectin-4, it is worth noting that no studies have yet systematically investigated the hotspots, cutting-edge directions, and tissue expression of this target using a combination of bibliometric analysis and bioinformatics methods. Findings reveal growing interest in Nectin-4's role in cancer immunotherapy and ADC development. Urothelial carcinoma remains the primary focus, with breast and bladder cancers gaining traction. Key research priorities include optimizing ADC safety profiles, particularly managing cutaneous adverse events. Notably, dual targeting strategies combining Nectin-4 with TROP-2 show promise for next-generation ADC therapies. The study highlights evolving clinical needs, from target validation to treatment optimization, positioning Nectin-4 as a versatile biomarker bridging multiple cancer research domains. These insights emphasize the protein's translational potential while underscoring the importance of balancing therapeutic efficacy with toxicity management in ADC development.

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Introduction

NECTIN4, also called Poliovirus Receptor-Related Protein 4 (PVRL4), is a transmembrane protein part of the Nectins family of immunoglobulin-like molecules.[1] NECTIN4 is important for cell adhesion, cell proliferation, cell migration, and the creation of blood vessels. It promotes angiogenesis by interacting with integrin β4, activating the Src, PI3K, Akt, and inducible nitric oxide synthase (iNOS) signaling pathways.[2] In addition, NECTIN4 is highly expressed in various tumor types, including breast cancer,[3] lung cancer,[4] urothelial carcinoma,[5] colorectal cancer, pancreatic cancer, and ovarian cancer. Its high expression is closely associated with tumor initiation, progression, and prognosis.

Antibiotic-drug conjugates (ADCs) targeting NECTIN4 have become a research hotspot.[6] Enfortumab vedotin (brand name: Padcev®) is the first FDA-approved ADC targeting NECTIN4 to treat urothelial carcinoma.[6] This drug binds to NECTIN4 on the surface of tumor cells, undergoes endocytosis, releases cytotoxic agents, inhibits cell division, and induces apoptosis.[7] Other NECTIN4-targeted drugs under investigation include ETx-22,[8] developed by Emergence Therapeutics, and 9MW2821 by Mewi Biologics.[9] These drugs have demonstrated good antitumor activity and tolerability in preclinical and clinical studies.

Numerous reviews have summarized NECTIN-4 from multiple perspectives. For instance, Kaiyue Li elucidated its molecular mechanisms in oncogenesis, diagnostic potential, and therapeutic value as a target for drugs like enfortumab vedotin, particularly in urothelial carcinoma.[4] Mina Nikanjam[10] analyzed NECTIN-4 expression (membranous/cytoplasmic) and amplification across cancers, highlighting its role as a response biomarker and the clinical development of NECTIN-4-targeted agents. However, despite these advances, no study has yet combined bibliometric analysis to map research trends with pan-cancer transcriptomics to comprehensively evaluate NECTIN-4's mRNA expression across tumor and normal tissues – a critical gap for predicting adverse effects of NECTIN-4-directed therapies. Compared to traditional reviews, bibliometric analysis provides a more systematic approach to evaluating the current state of research in a particular field.[11] By quantitatively analyzing the number of NECTIN4-related publications, citation patterns, published journals, and author collaboration networks, it is possible to reveal development trends and research hotspots in the field, thereby providing references for subsequent research. Additionally, bibliometric analysis can help identify gaps in the research, guiding future research directions.

Therefore, this study aims to systematically review available research publications on the role of NECTIN4 in cancer, using bibliometric analysis. It seeks to explore the research progress that has been made, and provide suggestions for future research directions. This study hopes to offer

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new perspectives for a deeper understanding of the role of NECTIN4 in tumor biology and to promote further exploration in related fields.

Data and methods

Search strategy

The data for this study were sourced from the Web of Science Core Collection (WoS). Web of Science is a comprehensive literature retrieval platform encompassing high-quality academic publications across multiple disciplines and is widely used in scientific research and bibliometric analyses.[12] In this study, we employed the following search strategy: (((((((((TS=("Nectin Cell Adhesion Molecule 4")) OR TS=(Nectin-4)) OR TS=("Poliovirus Receptor-Like 4")) OR TS=(PVRL4)) NOT DT=(Retracted Publication)) NOT DT=(Editorial Material)) NOT DT=(Early Access)) NOT DT=(Correction)) NOT DT=(Letter)) NOT DT=(News Item))

The search was conducted on December 15, 2024, to ensure the inclusion of the most recent research findings and data. A total of approximately 492 relevant publications were retrieved. These publications included journal articles, conference papers, and other documents, providing a rich foundation for subsequent bibliometric analysis.

To explore the cutting-edge research trends and hotspots in the Nectin-4 field by 2025, we conducted a renewed search in the Web of Science database on April 11, 2025. The search timeframe was set from 2024 to 2025. Using the CiteSpace software, we filtered the search results by Article, Review, and Meeting Abstract, ultimately selecting 126 articles for analysis. For sensitivity analysis, these articles were sliced by month.

Time parameter settings

(1) Term co-occurrence analysis: Based on the annual distribution characteristics of the literature, first screen out the high-growth rate year intervals, and then use VOSviewer software to achieve network visualization analysis.
(2) Keyword heatmap: To fully present the development trajectory of the field, construct a heatmap covering the entire research cycle (2004–2024).
(3) Nectin-4 research transformation analysis: Use annual average time resolution, with the time range set from 2004 to 2024.
(4) Co-citation frontier detection: Use a monthly analysis slicing method, with the time range set from 2024 to 2022.

Software tools

R-bibliometrix package

The R-bibliometrix package[13] is a tool within the R programming language designed explicitly for bibliometric analysis. This package facilitated the exploration of the overall characteristics of NECTIN4-related data, including publication trends and author collaboration networks, thereby providing essential support for in-depth analysis.

HiscitePro

HiscitePro is a specialized bibliometric analysis tool that offers detailed information on academic literature. In this study, HiscitePro was utilized to obtain data on the annual publication volume of NECTIN4, the global average annual citation frequency, and the number of publications and total global citations by countries/regions, institutions, and authors. This comprehensive data collection formed the basis for a thorough analysis.

CiteSpace

CiteSpace[14]is a visualization tool for scientific literature, particularly adept at revealing the knowledge structure of research fields. This study employed CiteSpace to create dual overlay maps of journals, perform co-citation analysis of references, and conduct keyword burst detection. These analytical methods enhanced the understanding key themes and hotspots in NECTIN4 research.

VOSviewer

VOSviewer[15] is used for constructing and visualizing bibliometric networks and is commonly applied to analyze citation relationships and keyword co-occurrence. In this study, VOSviewer was utilized to generate keyword co-occurrence network analyses and keyword-time overlay networks to identify the evolving trends in research topics.

Pajek

Pajek is software suited for handling extensive network data and is primarily used for complex network analysis and visualization. In this study, Pajek was employed to create keyword clustering maps, illustrating the relationships and clustering of different keywords. This provided more profound insights into the research on NECTIN4.

Pan-cancer analysis

We paired the regular tissue TPM expression from GTEx with the tumor TPM expression from TCGA (from the tcga_RSEM_gene_tpm and gtex_RSEM_gene_tpm datasets in the UCSC Xena database). To ensure accuracy and minimize the impact of anatomical factors, we only retained the primary tumor tissues from TCGA to pair with GTEx data. The data were standardized by transforming them into unitless Z-scores using the formula $(x-\mu)/\sigma$ for each tumor, ensuring uniform data standardization. Z-scores less than −3 or greater than three were considered outliers, and these outliers were removed. After removing the outliers, tumors were included in the analysis if there were at least three standard samples. Wilcoxon Rank Sum Tests were used to compare the statistical differences in expression levels between tumors and normal tissues in the dataset.

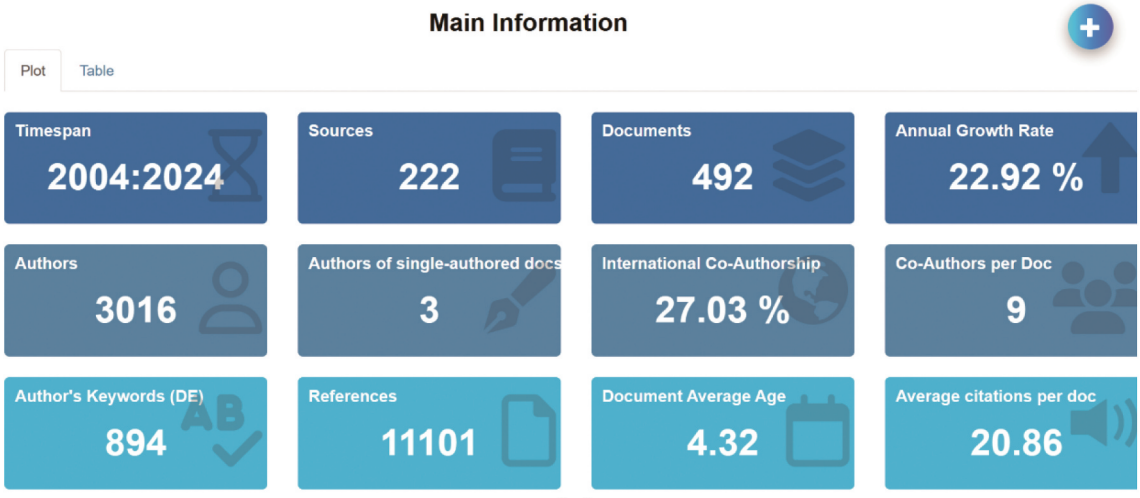
Results

External characteristics of NECTIN4 research

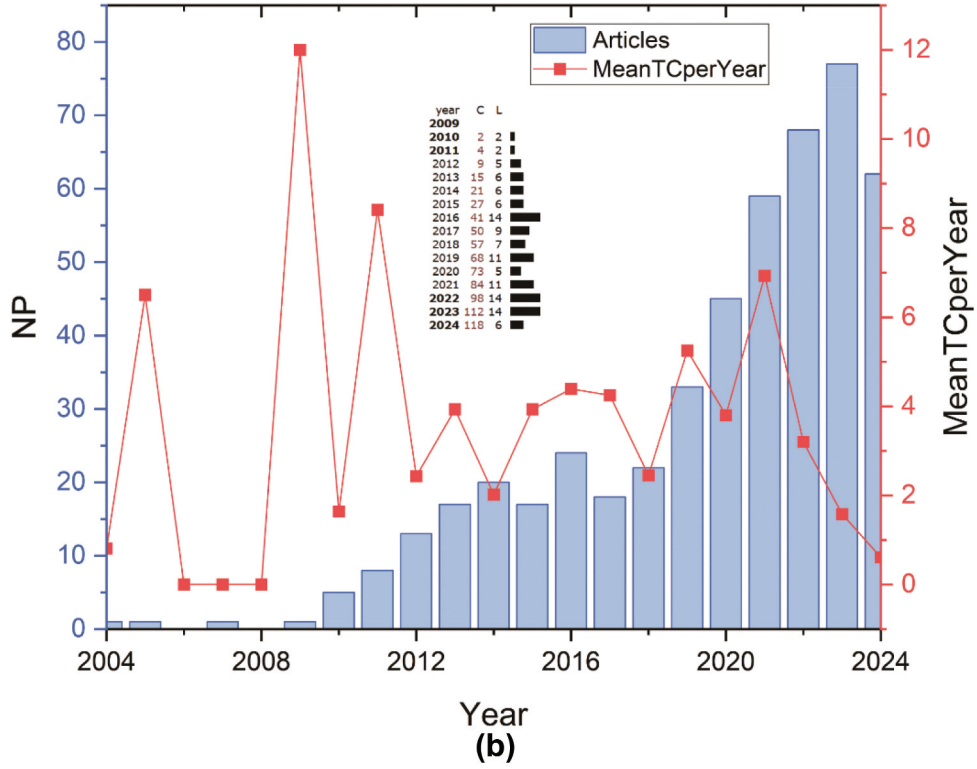
Figure 1a illustrates that in the NECTIN4 research field, 492 papers were published from 2004 to 2024 across 222 journals. This data indicates an impressive average annual growth rate of 22.92%, reflecting the rapid development trend of this research area. These 492 publications cited 11,101 distinct

references, demonstrating the extensive and rich knowledge base within the field. Additionally, 3,016 authors worldwide have contributed to NECTIN4-related research, with an international collaboration rate of 27.03%. This proportion suggests that although there is a certain level of international cooperation, there is still room for improvement. Notably, the average number of citations per paper is 20.86, indicating that the research outcomes in this field have garnered relatively good recognition and influence within the academic community.

Figure 1b displays the distribution of annual publication counts and average annual citation frequencies in the NECTIN4 field. Starting in 2017, the number of publications in this area significantly increased, reaching its peak in 2023. Interestingly, despite only one paper being published in 2009, the global average annual citation frequency for that year was the highest among all years. Through analysis with HiscitePro, we identified that Daigo authored this paper, Yataro et al.,[16] and published it in 2009. The study focused on gene expression profiling in lung cancer, revealing the trans-activation phenomenon of Nectin-4 in non-small cell lung cancer (NSCLC). The research indicated that high expression of Nectin-4 is associated with poor prognosis and that serum levels of Nectin-4 could serve as a potential biomarker and therapeutic target for NSCLC.



(a)



(b)

Figure 1. External characteristics of NECTIN4 research and annual publication analysis. (a) Analysis of the input.Zip data using the R-bibliometrix package to obtain the external characteristics of NECTIN4-related literature. (b)Utilizing HiscitePro to acquire the annual publication counts and global average annual citation frequencies and employing origin 2024 to create a dual Y-axis bar-line chart that illustrates the relationship between the annual number of publications and the global average annual citation frequencies.

Journal characteristics analysis

Figure 2a illustrates that the core journals in the NECTIN4 research field include Cancer Research, Journal of Virology, Cancers, Journal of Clinical Oncology, and Viruses-Basel.

Journal coupling analysis identifies journals with similar disciplinary or specialized content by the number of shared references in their bibliographies, thereby visualizing the similarity in their research content.[17] Figure 2b displays the journal coupling within the NECTIN4 field, where the colors correspond to each journal's average publication year of NECTIN4-related articles. The nodes on the left side predominantly exhibit more fabulous colors, indicating that these journals have earlier average publication years compared to those on the right side. The journals on the left are mainly related to virology, with the Journal of Virology having the most significant node. In contrast, the journals on the right primarily focus on oncology, with the Journal of Clinical Oncology having the most significant node. This result

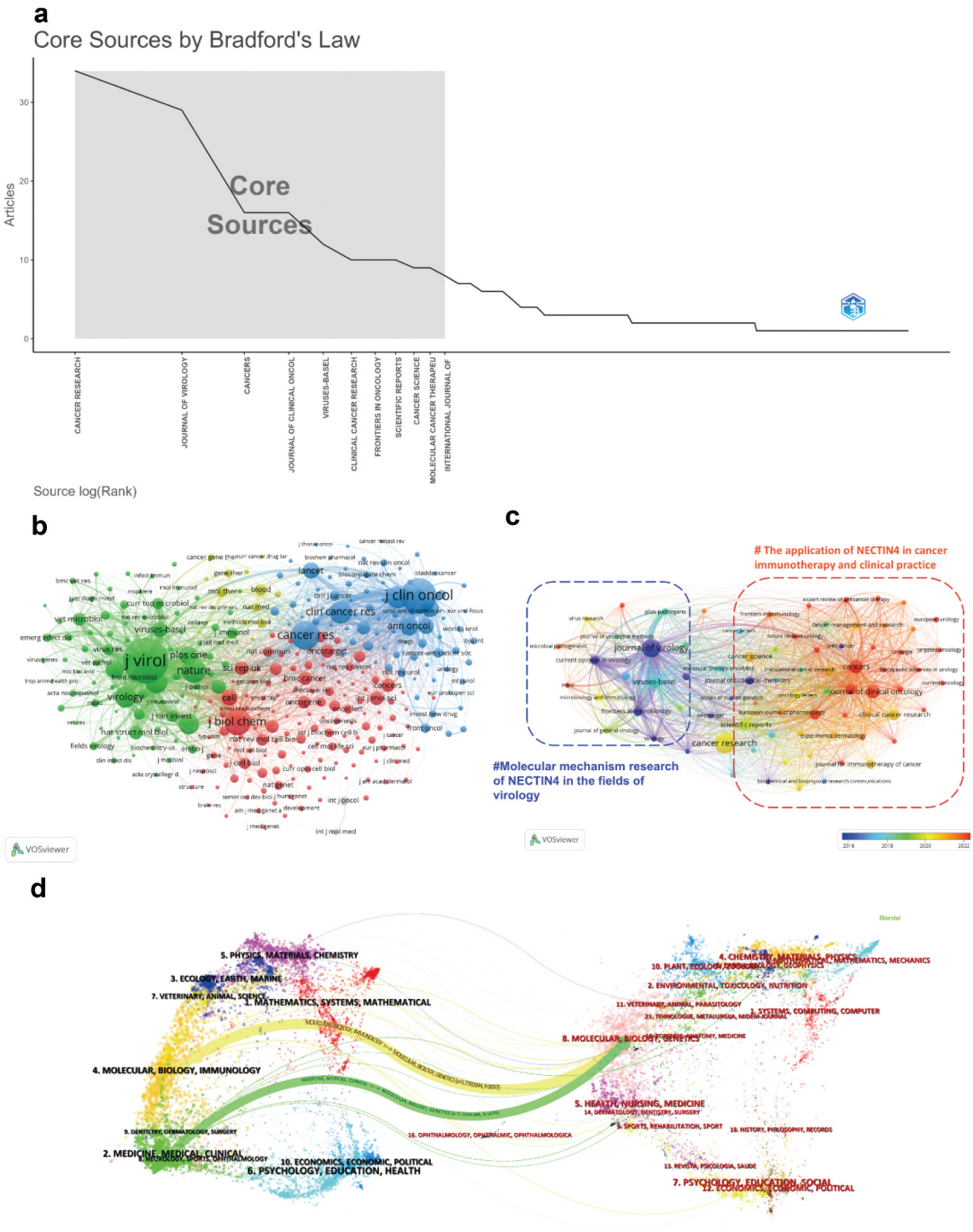


Figure 2. Distribution of NECTIN4 in academic journals. (a) Bradford's law analysis of core journals using the bibliometrix package. (b) Journal coupling analysis using VOSviewer, with different colors representing clusters. (c) Journal co-citation analysis using VOSviewer, primarily divided into two clusters. (d) Journal dual-map overlay analysis using CiteSpace.

suggests that early research in the NECTIN4 field primarily focused on the molecular mechanisms of NECTIN4 as a virological target. As understanding its molecular mechanisms deepened, the focus of NECTIN4 research shifted toward the oncology field, particularly in urological oncology. Concurrently, there has been an increasing number of studies on tumor immunology and clinical trials.

The dual-map overlay of journals,[18] designed by Chen Chaomei and Leydesdorff, aims to reveal patterns between scientific domains and the global map of scientific literature. The background map depicts the interconnections among over 10,000 scientific journals, further grouped into regions representing disciplinary-level publications and citation activities.[19] Figure 2a presents two citation relationship curves originating from "Molecular, Biology, Immunology" and "Medicine, Medical, Clinical," both pointing toward "Molecular, Biology, Genetics." This indicates that the primary research foundation of NECTIN4 lies in molecular biology and genetics. Over time, it has evolved to encompass molecular biology, immunology, medicine, and clinical disciplines.

Keyword analysis

Based on Figure 1b, the number of publications in the NECTIN4 field has consistently exceeded 20 papers annually from 2018 to the present, indicating rapid growth. Utilizing VOSviewer's term co-occurrence analysis, we explored the research directions from 2018 to 2024. Figure 3a reveals three distinct clusters. The red cluster primarily focuses on the "Application of Antibody-Drug Conjugates and Immunotherapy in Urothelial Carcinoma," encompassing keywords such as "enfortumab vedotin," "antibody," "drug," "conjugate," "chemotherapy," "urothelial carcinoma," "antibody drug," "metastatic urothelial," "carcinoma," and "clinical trial." The green cluster centers on "Measles Virus and Cellular Receptor Interactions and Their Role in Host Infection," with related keywords including "receptor," "gene," "infection," "molecule," "measles virus," "slam," "pvrl4," and "interaction." The blue cluster pertains to "The Role of NECTIN4 in Tumor Metastasis and Cell Adhesion and Its Research as a Therapeutic Target," involving keywords such as "cell line," "expression pattern," and "nectin cell adhesion molecule."

Figure 3b illustrates the annual keyword heatmap from 2004 to 2024, representing the keyword intensity (number of citations in the given year divided by the total citations). Using the bibliometrix package and ComplexHeatmap, we generated a heatmap to showcase research hotspots across different years. In Figure 3c, red dashed borders highlight the enduring research themes from 2020 to 2024, including "Target Therapy," "Sacituzumab Govitecan," "Urothelial Carcinoma," "Bladder Cancer," "Antibody-Drug Conjugate," "Enfortumab Vedotin," and "Immunotherapy." This indicates that these keywords represent emerging and consistently focused frontier research areas.

Additionally, the study employed the Burst algorithm to analyze keyword emergence. Figure 4b displays the initiation times of keyword bursts. Apart from a brief surge in "breast cancer" between 2016 and 2017, the keywords before 2020 primarily included "cellular receptor," "hemagglutinin," "activation molecule slam," "slam," and "canine distemper virus." However, these keywords showed no significant burst activity up to 2024. Multiple keywords burst in 2020 and continued to exhibit intense activity through 2024. These include tumor types such as "bladder cancer," "urothelial carcinoma," and "breast cancer;" clinical research methods like "multicenter" and "open-label;" drug-related keywords including "enfortumab vedotin," "sacituzumab govitecan," and "pembrolizumab;" and drug research methods focused on "antibody-drug conjugate." These sustained keyword bursts reflect the ongoing and intensifying focus on specific tumor types, advanced clinical research methodologies, and developing and applying targeted antibody-drug conjugates within the NECTIN4 research landscape.

Co-citation analysis of references

This study utilized CiteSpace's co-citation analysis to identify shifts in research directions within the NECTIN4 field (Figure 4a). Cluster #0 contained the most significant references and was identified as "Advanced Urothelial Carcinoma." According to the Cluster Mountain view, Cluster #0 remains a consistently researched cluster from 2020 to 2024. Additionally, Cluster #0 includes the highest number of highly cited references among all identified clusters, suggesting that advanced urothelial carcinoma is likely the most influential research direction within the NECTIN4 target field.

Figure 4a illustrates the formation of two major research clusters interconnected by two seminal publications. In 2014, Sebastien Delpeut et al.[20] reviewed PVRL4 (Nectin-4) as an epithelial cell receptor for the paramyxovirus family (including measles, canine distemper, and sheep poxvirus). They highlighted its role not only in viral pathogenic mechanisms but also in its expression in various adenocarcinomas (lung, breast, and ovarian cancers), positioning it as a potential target for cancer therapy. The study suggested that measles virus vaccine strains could serve as oncolytic platforms to target and destroy PVRL4-expressing cancer cells specifically. In 2016, Sarah Aref et al.[21] reviewed the role of Nectin-4 (PVRL4) as an epithelial cell receptor for measles virus (MV) in oncolytic virus therapy. They demonstrated that Nectin-4 facilitates the preferential infection and destruction of tumor cells expressing Nectin-4, thereby enhancing MV's tumor specificity and oncolytic efficacy.

The cluster mountain view in Figure 4b illustrates that clusters #0 ("Advanced Urothelial Carcinoma"), #1 ("Therapeutic Target"), and #2 ("Overall Survival") are the sustained research directions from 2022 to 2024.

Sensitivity analysis

To explore the research frontiers of 2024, we limited the time range to 2024–2025 and performed monthly data slicing for co-citation analysis (Figure 5). According to cancer type classification, the research frontiers of Nectin-4 from 2024 to 2025 cover the following areas: #0 urothelial carcinoma, #4 treating gynecologic cancer, #8 ovarian cancer patient ascites, #11 kidney cancer, #13 bladder cancer, #14 prostatic adenocarcinoma, and #21

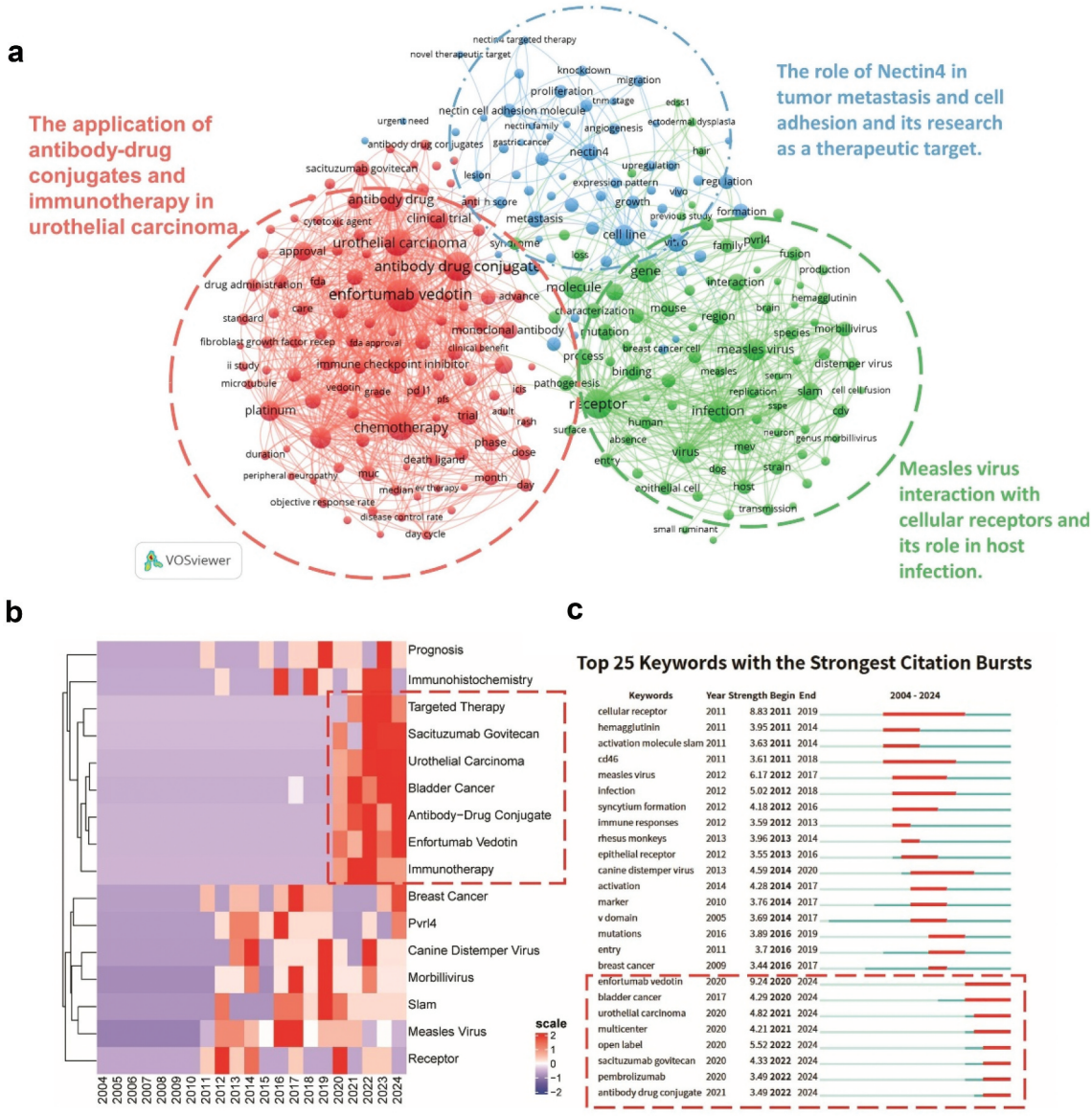


Figure 3. Research directions and hotspot analysis. (a) Co-occurrence analysis of author keywords from 2018 to 2024. Nodes with the same color belong to the same cluster, and the node size represents the frequency of the keyword's occurrence. (b)ggplot2 keyword hotspot matrix analysis. (c) CiteSpace keyword burst analysis.

cutaneous adnexal carcinoma. Additionally, the research directions of #2 autophagy inhibitor, #6 managing potential adverse events, #7 platinum ineligibility criteria, and #9 nuclear medicine were also identified.

Expression of NECTIN4 in pan-cancer and tissues

The above results indicate that the NECTIN4 target has been extensively studied in urothelial carcinoma. To investigate the expression of this target in other cancers, we conducted a visual analysis of NECTIN4 expression levels in normal and tumor tissues using the TCGA and GTEx databases (Figure 6a–b). The analysis revealed that NECTIN4 is significantly upregulated in multiple tumor types compared to normal tissues, including bladder urothelial carcinoma, breast cancer, cholangiocarcinoma, colon cancer, diffuse large B-cell lymphoma, glioblastoma, clear cell renal cell carcinoma, liver cancer, lung adenocarcinoma, lung squamous cell carcinoma, ovarian cancer, pancreatic cancer, pheochromocytoma, paraganglioma, prostate cancer, gastric cancer, thyroid cancer, testicular cancer, thymoma, endometrial cancer, and uterine cancer. These findings demonstrate that the NECTIN4 target exhibits widespread upregulation across a diverse range of tumor types, highlighting its extensive potential as a therapeutic target beyond urothelial carcinoma and underscoring its potential therapeutic value and broad application prospects in oncology.

Discussion

The foundation of NECTIN-4 focused-research

Our journal coupling analysis revealed the multidisciplinary nature of NECTIN4 research, with its research trajectory originating from molecular biology and genetics

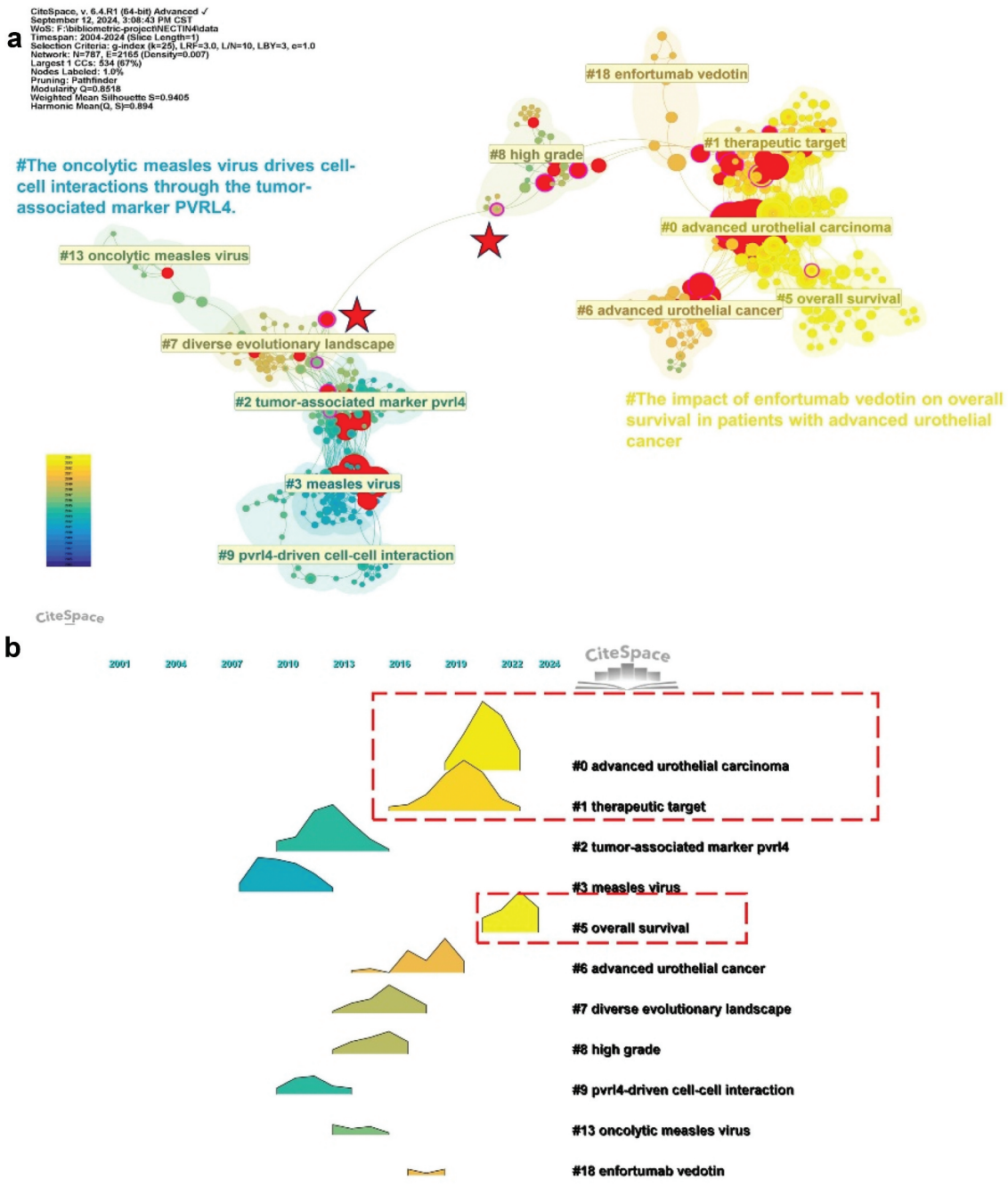


Figure 4. Co-citation analysis of references. (a) Co-citation analysis of references using CiteSpace. The clustering colors transition from cool to warm, representing the average publication year of clusters from older to newer. (b) CiteSpace reference clustering mountain plot.

foundations and gradually expanding into immunology and clinical medicine. Early studies concentrated on virology, particularly the area represented by the Journal of Virology. At the same time, recent research has shifted toward oncology, especially urological tumors, such as those published in the Journal of Clinical Oncology.

The green cluster primarily revolves around the measles virus and its interactions with cellular receptors, elucidating viral infection mechanisms. However, Figure 4a indicates that research in this cluster occurred in earlier years. The blue cluster was identified as "The role of Nectin4 in tumor metastasis and cell adhesion and its research as a therapeutic target." The keywords in this cluster mainly focus on tumor biology, cell adhesion mechanisms, and their impact on cancer progression, particularly molecules related to the nectin family, including nectin4. These keywords encompass various aspects, such as tumor cell proliferation, migration, metastasis, and drug resistance, revealing the importance of intercellular interactions in tumorigenesis. This direction likely represents a transition in NECTIN4 research from fundamental to clinical studies and tumor drug development.

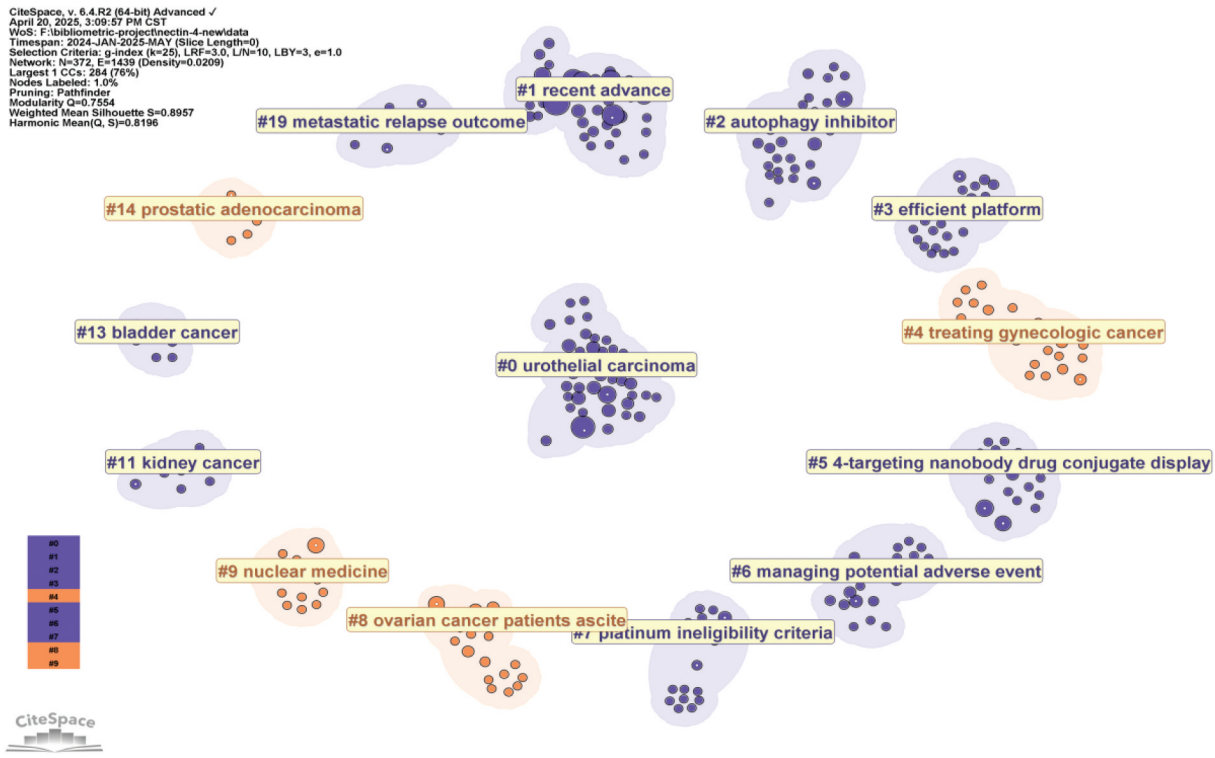


Figure 5. Analysis of research frontiers in 2024–2025. Circular layout analysis using CiteSpace.

The application of antibody-drug conjugates in urothelial carcinoma

The keywords of the red cluster are mainly focus on Antibody-Drug Conjugates (ADCs) and their use in advanced urothelial carcinoma (UC), high-grade bladder cancer, and "metastatic urothelial carcinoma." ADCs have emerged as a promising cancer treatment modality. ADCs consist of monoclonal antibodies linked to potent cytotoxic drugs via chemical linkers. This molecular design combines antibodies' targeting specificity and longer circulation half-life with highly cytotoxic drugs for tumor cells, which are often too toxic when used alone.[22] As an aberrantly expressed type I transmembrane protein in various cancer types, nectin-4 (also known as PVRL4) has become a promising target in ADC research and development.[23] The most prominent ADC drug targeting NECTIN4 is Enfortumab Vedotin (EV), the first nectin-4 ADC approved by the FDA for metastatic urothelial carcinoma. EV consists of a fully human monoclonal antibody that explicitly recognizes nectin-4 and monomethyl auristatin E (a drug that disrupts microtubule formation). Targeted delivery of monomethyl auristatin E results in cell cycle arrest and apoptosis.[24]

Additionally, combination therapy research is gaining momentum, primarily focusing on "immune checkpoint inhibitors" and "chemotherapy." Combination therapies have been shown to improve treatment outcomes further. In 2024, the New England Journal of Medicine conducted a Phase III, global, open-label, randomized trial comparing the efficacy and safety of enfortumab vedotin plus pembrolizumab versus platinum-containing chemotherapy in previously untreated patients with locally advanced or metastatic urothelial carcinoma.[25] In addition to the classic Enfortumab Vedotin, 9MW2821, SYS6002, and BT8009 are also NECTIN4-based ADC drugs. 9MW2821 is a monoclonal antibody-drug conjugate (ADC) that delivers monomethyl auristatin E to nectin-4-expressing cells.[9,26] SYS6002 (CRB-701) is a novel ADC targeting Nectin-4, utilizing third-generation, specifically cleavable linkers and novel conjugation chemistry.[27] This technology aims to establish a stable linker between the antibody and drug, producing ADCs with a uniform drug-antibody ratio of 2.0 and reducing the concentration of free monomethyl auristatin E (MMAE) to improve known drug-related toxicities. SYS6002 (CRB-701) also includes a novel monoclonal antibody with an extended half-life, supporting a once-every-three-week dosing regimen. Encouragingly, at equivalent dose levels, SYS6002 (CRB-701) exhibited a longer ADC half-life and lower free MMAE exposure than EV. SYS6002 (CRB-701) has shown promising antitumor activity and a favorable safety profile in patients with advanced nectin-4-positive solid tumors. BT8009 (Bicycle Toxin Conjugate, BTC) consists of a bicyclic peptide that binds Nectin-4, a cleavable linker system, and the cell-penetrating toxin monomethyl auristatin E (MMAE).[28] As a small, hydrophilic peptide-based drug, BT8009 can rapidly diffuse from the systemic circulation, penetrate tissues to reach tumors, and target tumor cells.[29] It is excreted via the kidneys, with a half-life of 1–2 hours (in rats and non-human primates). These physicochemical and pharmacokinetic characteristics distinguish BT8009 from ADCs and may provide benefits in tumor penetration and reduced systemic exposure.

The management of adverse events associated with Nectin4 antibody-drug conjugates

The red cluster in Figure 3 involves "adverse events, toxicity, and side effects (such as fatigue and peripheral

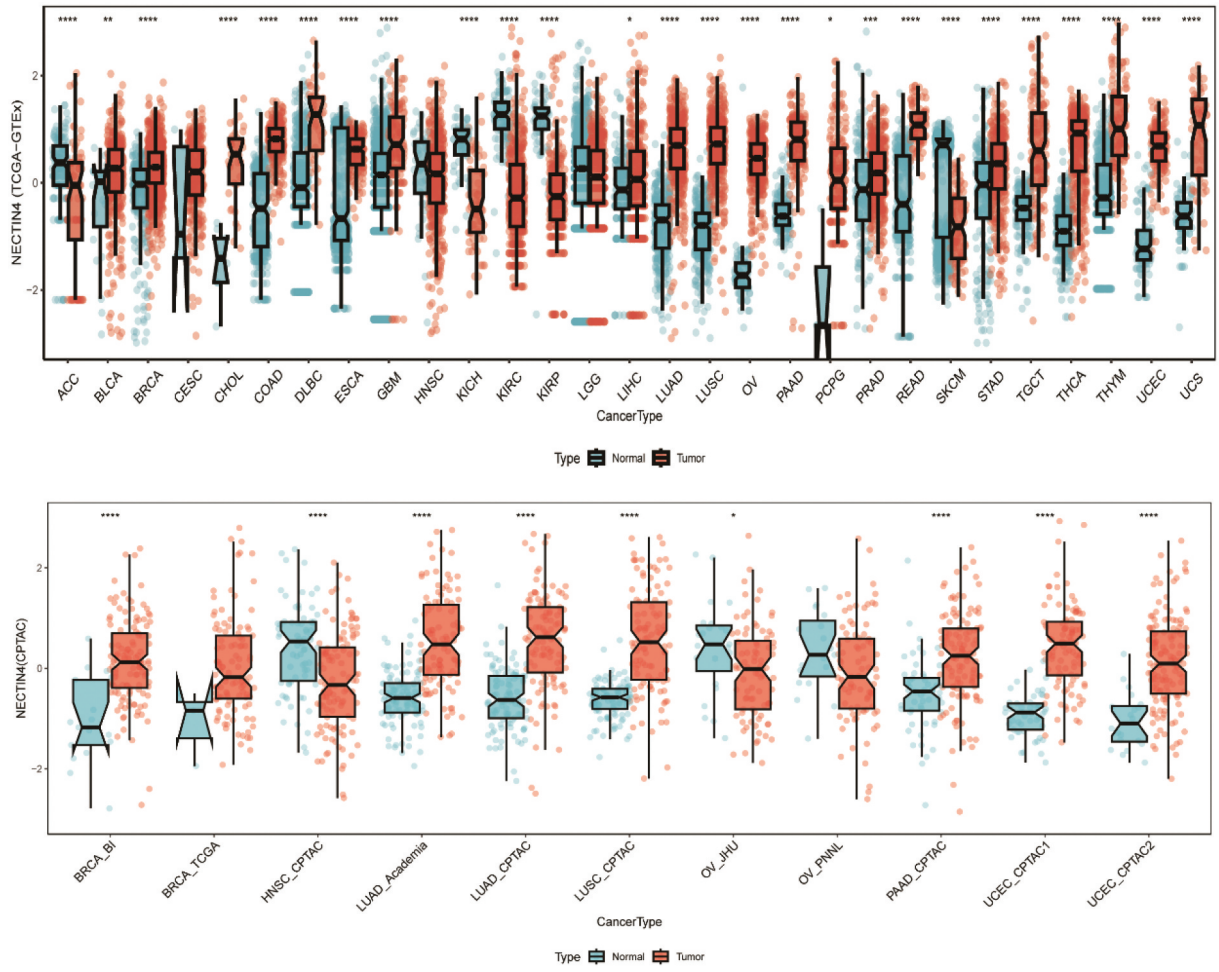


Figure 6. mRNA and protein expression levels of NECTIN4 in pan-cancer. (a) mRNA expression levels of NECTIN4 in TCGA and GTEx. (b) Protein expression levels of NECTIN4 in pan-cancer. *wilcoxon rank sum tests measured p-value*.

neuropathy)," and Figure 5 shows "#6 managing potential adverse events." This indicates that with the successful development of NECTIN4-targeted antibody drugs, the potential adverse reactions associated with these antibodies are increasingly gaining attention. Studies on Cluster 6 have shown that patients treated with enfortumab vedotin were diagnosed with chemotherapy-induced toxic erythema, which improved after twice-daily application of 0.1% triamcinolone acetonide ointment without discontinuing EV infusion.[30] The FDA has approved enfortumab vedotin-ejfv in combination with pembrolizumab for locally advanced or metastatic urothelial carcinoma.[31] However, Blaine Brower et al.[31] summarized the potential adverse reactions of this combination therapy, including rashes, peripheral neuropathy, hypertension and diabetes, pneumonia, gastrointestinal reactions, fatigue, and ocular disease symptoms and management strategies. In addition, the supplementary figure shows the RNA levels of NECTIN genes in different tissues based on HPA and GTEx transcriptomic data, indicating that the skin has the highest NECTIN-4 expression (Supplementary Figure S1a). This result also suggests that antibodies targeting NECTIN4 may lead to skin adverse reactions.

The research hotspots of the Nectin4 target

In addition to the classic urothelial carcinoma, breast cancer has gradually become a research hotspot. Studies have found that NECTIN4 expression is higher in triple-negative breast cancer (TNBC) and is associated with poorer overall survival. In multivariate analysis, high PVRL4 mRNA expression was an independent adverse prognostic factor for metastasis-free survival (MFS) in TNBC.[32] The high expression level in normal skin may lead to skin toxicity associated with the approval of enfortumab vedotin, which requires careful consideration, as ADCs targeting Nectin-4 are being developed for breast cancer.[3] With the research on the mechanism of action of NECTIN4, clinical research methods such as multicenter and open-label studies are gradually becoming clinical research strategies for this target.[33–35] The TROP-2 antibody-drug conjugate Sacituzumab govitecan has also been identified,[36] with studies indicating that TACSTD2/TROP2 and NECTIN-4 are widely expressed in advanced urothelial carcinoma (aUC)[37] and are independent of FGFR3 alterations or PD-L1 expression. Therefore, they represent targets suitable for antibody-drug conjugate (ADC) therapy in the majority of aUC patients. Future research on advanced

urothelial carcinoma will involve developing dual-target antibodies targeting TROP-2 and NECTIN4.

The frontier of NECTIN-4 research

The role of Nectin-4 in gynecological tumors

Sensitivity analysis for 2024–2025 identifies gynecological tumors as a key research frontier. The core citation in Cluster #5 is Silverstein's review on antibody-drug conjugates (ADCs) for gynecologic cancers. Exatecan, developed by Eli Lilly and Company, targets DNA topoisomerase I and the cell adhesion molecule Nectin-4, currently in Phase I clinical trials for ovarian, endometrial, and cervical cancers.[38] Additionally, Cluster #8 highlights ovarian cancer patient ascites, with the primary citation demonstrating that Nectin-4-targeted peptide N4-P10 enhances cisplatin cytotoxicity by inhibiting tumor spheroid formation, offering a novel strategy to overcome chemoresistance[39] Nectin-4, a critical molecule in cancer progression and metastasis, is strongly associated with peritoneal spread and poor prognosis in high-grade serous ovarian carcinoma (HGSOC). Its specificity and sensitivity as a biomarker surpass those of CA-125. Furthermore, nanocrystalline quinacrine inhibits cervical cancer stem cell proliferation via Nectin-4, while endometrial cancer detection shows 95.4% specificity and 82.81% sensitivity, positioning it as a promising theranostic biomarker.[40]

The role of Nectin-4 in renal cancer

The identified cluster pertains to "KIDNEY CANCER." A key study by Clara Cerrato et al. reports that males showed a survival advantage in second-line treatment with ADC-Nectin-4 for transitional cell carcinoma (TCC). In contrast, androgen deprivation therapy (ADT) versus Nectin-4-targeted therapy favored male patients.[41]

The role of Nectin-4 in bladder cancer

In bladder cancer histological variants (BCDD), Nectin-4 is highly expressed in squamous/plasmacytoid subtypes, guiding enfortumab vedotin therapy. Other features include high PD-L1 positivity in sarcomatoid variants, a 50% RB1 mutation rate in small-cell types, and elevated TEC expression in immunotherapy responders.[42]

The role of Nectin-4 in cutaneous adnexal carcinoma

Nectin-4 is significantly overexpressed in cutaneous adnexal carcinomas, particularly sebaceous carcinoma, suggesting enfortumab vedotin as a potential therapeutic option.[43]

Development of Nectin-4-targeted nanodrugs

Using phage display technology, Yue Wu[44] developed a trivalent humanized nanobody-drug conjugate (huNb26/Nb26-Nbh-MMAE) targeting Nectin-4. This conjugate exhibits superior tumor targeting, cytotoxicity, rapid tissue penetration, and high tumor uptake in gastric cancer mouse models, demonstrating dose-dependent antitumor effects.

Pan-cancer analysis of the NECTIN4 target

While the NECTIN4 target has been extensively studied in urothelial carcinoma, its expression in other types of tumors is equally noteworthy.[45] Through visual analysis of the TCGA and GTEx databases, we found that NECTIN4 is significantly upregulated in various cancers, including bladder urothelial carcinoma, breast cancer, cholangiocarcinoma, and colon cancer, among others. This finding validates the broad applicability of NECTIN4 as a potential biomarker and suggests its possible significant role in the development and progression of multiple cancers. In particular, in common malignant tumors such as breast cancer, lung adenocarcinoma, and ovarian cancer, the upregulation of NECTIN4 expression may be closely related to tumor cell proliferation, invasion, and metastatic capabilities. This implies that NECTIN4 can serve as a candidate target for targeted therapy and may provide clinical value in predicting the prognosis of tumor patients. Furthermore, given the differences in immune microenvironment, electrophysiological characteristics, and transcriptomic features among different tumor types, changes in NECTIN4 expression may reflect the biological complexity of these tumors' behaviors.

Limitations

First, the data source was limited to the Web of Science Core Collection, excluding other important databases such as PubMed, Scopus, and Google Scholar. Second, due to the study cutoff date, the most recent Nectin-4 research data may not be included. Third, in terms of research depth, we did not integrate multi-omics analysis of the Nectin-4 target using cutting-edge technologies like single-cell sequencing and spatial transcriptomics.

Conclusion

The bibliometric analysis reveals a consistent increase in NECTIN-4-related publications from 2018 to 2024, though international collaboration remains limited. Notably, 2009 marked the peak year for total citations in this field. Journal characteristics and dual-map overlay analyses demonstrate a clear evolution in NECTIN-4 research: shifting from its initial focus as a measles virus receptor and investigations into tumor metastasis/cell adhesion mechanisms, toward current applications in tumor immunology and clinical translation of Nectin-4-targeting antibody-drug conjugates (ADCs).

Keyword timeline analysis identified Sacituzumab Govitecan and its combination therapies as predominant research themes during 2020–2024. Advanced urothelial carcinoma persists as the most studied malignancy in this domain. Importantly, given Nectin-4's high expression in normal tissues like skin, management of cutaneous adverse events (particularly rash) induced by Nectin-4-targeting ADCs has emerged as a novel research priority. Sensitivity analysis and pan-cancer bioinformatics further validate Nectin-4 overexpression in various tumors including gynecological cancers, skin adnexal carcinomas, and bladder cancer, providing a rationale for developing ADC therapies across multiple cancer types.

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No potential conflict of interest was reported by the author(s).

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Ethics approval and consent to participate

The data were obtained from the Clarivate Analytics database and did not involve ethical considerations.

Data availability statement

All raw data and code are available upon request.

References

1. Heath EI, Rosenberg JE. The biology and rationale of targeting nectin-4 in urothelial carcinoma. Nat Rev Urol. 2021;18(2):93–103. doi: 10.1038/s41585-020-00394-5.
2. Mühlebach MD, Mateo M, Sinn PL, Prüfer S, Uhlig KM, Leonard VH, Navaratnarajah CK, Frenzke M, Wong XX, Sawatsky B, et al. Adherens junction protein nectin-4 is the epithelial receptor for measles virus. Nature. 2011;480(7378):530–533. doi: 10.1038/nature10639.
3. Lattanzio R, Ghasemi R, Brancati F, Sorda RL, Tinari N, Perracchio L, Iacobelli S, Mottolese M, Natali PG, Piantelli M, et al. Membranous nectin-4 expression is a risk factor for distant relapse of T1-T2, N0 luminal-A early breast cancer. Oncogenesis. 2014;3(9):e118. doi: 10.1038/oncsis.2014.32.
4. Li K, Zhou Y, Zang M, Jin X, Li X. Therapeutic prospects of nectin-4 in cancer: applications and value. Front Oncol. 2024;14:1354543. doi: 10.3389/fonc.2024.1354543.
5. Klümper N, Tran NK, Zschäbitz S, Hahn O, Büttner T, Roghmann F, Bolenz C, Zengerling F, Schwab C, Nagy D, et al. NECTIN4 amplification is frequent in solid tumors and predicts enfortumab vedotin response in metastatic urothelial cancer. J Clin Oncol. 2024;42(20):2446–2455. doi: 10.1200/JCO.23.01983.
6. Moretto R, Germani MM, Giordano M, Conca V, Proietti A, Niccoli C, Pietrantonio F, Lonardi S, Tamburini E, Zaniboni A, et al. Trop-2 and nectin-4 immunohistochemical expression in metastatic colorectal cancer: searching for the right population for drugs' development. Br J Cancer. 2023;128:1391–1399. doi: 10.1038/s41416-023-02180-7.
7. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, Matsubara N, Vulsteke C, Castellano D, Wu C, et al. Enfortumab Vedotin in Previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384(12):1125–1135. doi: 10.1056/NEJMoa2035807.
8. Lopez M, Crompot E, Josselin E, Farina A, Rubis M, Castellano R, Fares J, Wehbe M, Collette Y, Charafe E, et al. Etx-22, a novel nectin-4–Directed antibody–drug conjugate, demonstrates safety and potent antitumor activity in low-nectin-4–Expressing tumors. Cancer Res Commun. 2024;4(11):2998–3012. doi: 10.1158/2767-9764.CRC-24-0176.
9. Zhou W, Fang P, Yu D, Ren H, You M, Yin L, Mei F, Zhu H, Wang Z, Xu H, et al. Preclinical evaluation of 9MW2821, a site-specific monomethyl auristatin E–based antibody–drug conjugate for treatment of nectin-4–expressing cancers. Mol Cancer Ther. 2023;22(8):913–925. doi: 10.1158/1535-7163.MCT-22-0743.
10. Nikanjam M, Pérez-Granado J, Gramling M, Larvol B, Kurzrock R. Nectin-4 expression patterns and therapeutics in oncology. Cancer Lett. 2025;622:217681. doi: 10.1016/j.canlet.2025.217681.
11. Goerlandt F, Li J. Forty years of risk analysis: a scientometric overview. Risk Anal. 2022;42(10):2253–2274. doi: 10.1111/risa.13853 .
12. Jin J, Wan Y, Shu Q, Liu J, Lai D. Knowledge mapping and research trends of IL-33 from 2004 to 2022: a bibliometric analysis. Front Immunol. 2023;14:1158323. doi: 10.3389/fimmu.2023.1158323.
13. Aria M, Cuccurullo C. Bibliometrix: an R-tool for comprehensive science mapping analysis. J Informetrics. 2017;11(4):959–975. doi: 10.1016/j.joi.2017.08.007.
14. Sabé M, Chen C, El-Hage W, Leroy A, Vaiva G, Monari S, Premand N, Bartolomei J, Caiolo S, Maercker A, et al. Half a century of research on posttraumatic stress disorder: a scientometric analysis. Curr Neuropharmacol. 2024;22(4):736–748. doi: 10.2174/1570159X22666230927143106.
15. van Eck NJ, Waltman L, van Eck NJ. Citation-based clustering of publications using CitNetExplorer and VOSviewer. Scientometrics. 2017;111(2):1053–1070. doi: 10.1007/s11192-017-2300-7.
16. Takano A, Ishikawa N, Nishino R, Masuda K, Yasui W, Inai K, Nishimura H, Ito H, Nakayama H, Miyagi Y, et al. Identification of nectin-4 oncoprotein as a diagnostic and therapeutic target for lung cancer. Cancer Res. 2009;69(16):6694–6703. doi: 10.1158/0008-5472.CAN-09-0016.
17. Shao B, Qin YF, Ren SH, Peng QF, Qin H, Wang ZB, Wang H-D, Li G-M, Zhu Y-L, Sun C-L, et al. Structural and temporal dynamics of mesenchymal stem cells in liver diseases from 2001 to 2021: a bibliometric analysis. Front Immunol. 2022;13:859972. doi: 10.3389/fimmu.2022.859972.
18. Chen C, Leydesdorff L. Patterns of connections and movements in dual-map overlays: a new method of publication portfolio analysis. J Assoc Inf Sci Technol. 2014;65(2):334–351. doi: 10.1002/asi.22968.

19. Wan Y, Shen J, Hong Y, Liu J, Shi T, Cai J. Mapping knowledge landscapes and emerging trends of the biomarkers in melanoma: a bibliometric analysis from 2004 to 2022. Front Oncol. 2023;13:1181164. doi: 10.3389/fonc.2023.1181164.
20. Delpeut S, Noyce RS, Richardson CD. The tumor-associated marker, PVRL4 (nectin-4), is the epithelial receptor for morbilliviruses. Viruses. 2014;6(6):2268–2286. doi: 10.3390/v6062268.
21. Aref S, Bailey K, Fielding A. Measles to the rescue: a review of oncolytic measles virus. Viruses. 2016;8(10):8. doi: 10.3390/v8100294.
22. Tsuchikama K, Anami Y, Syy H, Yamazaki CM. Exploring the next generation of antibody–drug conjugates. Nat Rev Clin Oncol. 2024;21(3):203–223. doi: 10.1038/s41571-023-00850-2.
23. Wang Y, Nan Y, Ma C, Lu X, Wang Q, Huang X, Xue W, Fan J, Ju D, Ye D, et al. A potential strategy for bladder cancer treatment: inhibiting autophagy to enhance antitumor effects of nectin-4-MMAE. Cell Death Dis. 2024;15(4):293. doi: 10.1038/s41419-024-06665-y.
24. Rosenberg J, Sridhar SS, Zhang J, Smith D, Ruether D, Flaig TW, Baranda J, Lang J, Plimack ER, Sangha R, et al. EV-101: a phase I study of single-agent enfortumab vedotin in patients with nectin-4–Positive solid tumors, including metastatic urothelial carcinoma. J Clin Oncol. 2020;38(10):1041–1049. doi: 10.1200/JCO.19.02044.
25. Powles T, Valderrama BP, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, Iyer G, Vulsteke C, Park SH, Shin SJ, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390(10):875–888. doi: 10.1056/NEJMoa2312117.
26. Fang P, You M, Cao Y, Feng Q, Shi L, Wang J, Sun X, Yu D, Zhou W, Yin L, et al. Development and validation of bioanalytical assays for the quantification of 9MW2821, a nectin-4-targeting antibody–drug conjugate. J Pharm Biomed Anal. 2024;248:116318. doi: 10.1016/j.jpba.2024.116318.
27. Ye D-W, Zhang J, Yang H, Yang J, Zheng T, Sun H, Sun Y, Li G, Liu F, Wan X, et al. Clinical update related to the first-in-human trial of SYS6002 (CRB-701), a next-generation nectin-4 targeting antibody drug conjugate. J Clin Oncol. 2024;42(16_suppl):3151–. doi: 10.1200/JCO.2024.42.16_suppl.3151.
28. Mudd GE, Scott H, Chen L, van Rietschoten K, Ivanova-Berndt G, Dzionek K, Brown A, Watcham S, White L, Park PU, et al. Discovery of BT8009: a nectin-4 targeting bicycle toxin conjugate for the treatment of cancer. J Med Chem. 2022;65(21):14337–14347. doi: 10.1021/acs.jmedchem.2c00065.
29. Rigby M, Bennett G, Chen L, Mudd GE, Harrison H, Beswick PJ, Van Rietschoten K, Watcham SM, Scott HS, Brown AN, et al. BT8009; a nectin-4 targeting bicycle toxin conjugate for treatment of solid tumors. Mol Cancer Ther. 2022;21(12):1747–1756. doi: 10.1158/1535-7163.MCT-21-0875.
30. Nagayama J, Inoue S, Sai H, Hayakawa A, Yuguchi Y, Suzuki T, Matsui H, Yuba T, Morishita K, Akamatsu S, et al. Treatment-related skin reactions in enfortumab vedotin as a surrogate marker of survival and treatment response. Int J Clin Oncol. 2024;30(2):267–276. doi: 10.1007/s10147-024-02672-3.
31. Zheng F, Du Y, Yuan Y, Wang Z, Li S, Xiong S, Zeng J, Tan Y, Liu X, Xu S, et al. Risk analysis of enfortumab vedotin: a real-world approach based on the FAERS database. Heliyon. 2024;10(18):e37544. doi: 10.1016/j.heliyon.2024.e37544.
32. Fujiyuki T, Amagai Y, Shoji K, Kuraishi T, Sugai A, Awano M, Sato H, Hattori S, Yoneda M, Kai C, et al. Recombinant SLAMblind measles virus is a promising Candidate for nectin-4-positive triple negative breast cancer therapy. Mol Ther - Oncolytics. 2020;19:127–135. doi: 10.1016/j.omto.2020.09.007.
33. Li S, Shi Y, Dong H, Guo H, Xie Y, Sun Z, Zhang X, Kim E, Zhang J, Li Y, et al. Phase 2 trial of enfortumab vedotin in patients with Previously treated locally advanced or metastatic urothelial carcinoma in China. Cancer Med. 2024;13(21):e70368. doi: 10.1002/cam4.70368.
34. Swiecicki PL, Yilmaz E, Rosenberg AJ, Fujisawa T, Bruce JY, Meng C, Wozniak M, Zhao Y, Mihm M, Kaplan J, et al. Phase II trial of enfortumab vedotin in patients with Previously treated advanced head and neck cancer. J Clin Oncol. 2024;43(5):578–588. doi: 10.1200/JCO.24.00646.
35. Brave MH, Maguire WF, Weinstock C, Zhang H, Gao X, Li F, Yu J, Fu W, Zhao H, Pierce WF, et al. FDA approval summary: enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. Clin Cancer Res. 2024;30(21):4815–4821. doi: 10.1158/1078-0432.CCR-24-1393.
36. Michel L, Jimeno A, Sukari A, Beck JT, Chiu J, Ahern E. Sacituzumab govitecan in patients with relapsed/refractory advanced head and neck squamous cell carcinoma: results from the phase 2 TROPiCS-03 basket study. Clin Cancer Res. 2024; doi: 10.1158/1078-0432.Ccr-24-2523.
37. Bahlinger V, Branz A, Strissel PL, Strick R, Lange F, Geppert CI, Klümper N, Hölzel M, Wach S, Taubert H, et al. Associations of TACSTD2/TROP2 and NECTIN-4/NECTIN-4 with molecular subtypes, PD-L1 expression, and FGFR3 mutational status in two advanced urothelial bladder cancer cohorts. Histopathology. 2024;84(5):863–876. doi: 10.1111/his.15130.
38. Silverstein J, Karlan B, Herrington N, Konecny G. Antibody–drug conjugates as targeted therapy for treating gynecologic cancers: update 2025. Curr Opin Obstet Gynecol. 2025;37(1):5–15. doi: 10.1097/GCO.0000000000001002.
39. Boylan KLM, Walz C, Schefter AM, Skubitz APN. A peptide derived from nectin-4 increases cisplatin cytotoxicity in cell lines and cells from ovarian cancer patients' ascites. Cancers (Basel). 2025;17(5):901. doi: 10.3390/cancers17050901.
40. Hooks O, Nagpal Y, Childers JT, Childers LT, Ahmad S. Theranostic implications of nectin-4 oncoprotein in gynecologic cancers: a review. Pathol, Res Pract. 2025;269:155913. doi: 10.1016/j.prp.2025.155913.
41. Cerrato C, Crocerossa F, Marchioni M, Giannarini G, Gupta S, Albiges L, Brouwer O, Albersen M, Fankhauser C, Grimm MO, et al. Effect of sex on the oncological outcomes in response to immunotherapy and antibody-drug conjugates in patients with urothelial and kidney cancer: a systematic review and a network meta-analysis. Eur Urology Oncol. 2024;7(5):1005–1014. doi: 10.1016/j.euo.2024.03.014.
42. Martini DJ, Case KB, Gratz D, Pellegrini K, Beagle E, Schneider T, Dababneh M, Nazha B, Brown JT, Joshi SS, et al. PD-L1 and nectin-4 expression and genomic characterization of bladder cancer with divergent differentiation. Cancer. 2024;130:3658–3670. doi: 10.1002/cncr.35465.
43. Cho WC, Saade R, Nagarajan P, Aung PP, Milton DR, Marques-Piubelli ML, Hudgens C, Ledesma D, Nelson K, Ivan D, et al. Nectin-4 expression in a subset of cutaneous adnexal carcinomas: a potential target for therapy with enfortumab vedotin. J Cutan Pathol. 2024;51(5):360–367. doi: 10.1111/cup.14579.
44. Wu Y, Zhu M, Sun B, Chen Y, Huang Y, Gai J, Li G, Li Y, Wan Y, Ma L, et al. A humanized trivalent nectin-4-targeting nanobody drug conjugate displays potent antitumor activity in gastric cancer. J Nanobiotechnol. 2024;22(1):256. doi: 10.1186/s12951-024-02521-5.
45. Tarantino P, Carmagnani Pestana R, Corti C, Modi S, Bardia A, Tolaney SM, Cortes J, Soria J-C, Curigliano G. Antibody–drug conjugates: smart chemotherapy delivery across tumor histologies. CA Cancer J Clin. 2022;72(2):165–182. doi: 10.3322/caac.21705.