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# Exploring the potential of bi-specific antibodies in cancer immunotherapy

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Bi-specific antibodies (BsAbs) represent a groundbreaking advancement in cancer immunotherapy, offering a novel approach to target and eliminate cancer cells by engaging two distinct antigens simultaneously. This review delves into the mechanistic foundations and clinical applications of BsAbs, highlighting their unique dual-targeting capabilities that bridge immune cells with malignant cells to enhance anti-tumor activity. We discuss the various types and design strategies of BsAbs, including their modular structures and engineering innovations that have propelled their efficacy and specificity. The review also examines preclinical and clinical trial data, showcasing the promising results and success stories in different cancer types. Despite their potential, BsAbs face challenges such as manufacturing complexities, stability issues, and toxicity concerns, which we explore alongside current solutions and regulatory considerations. By integrating the latest advancements and emerging trends, this review provides a comprehensive overview of BsAbs and their transformative role in the future of cancer therapy.

**Keywords:** bi-specific antibodies, cancer immunotherapy, dual-targeting, antibody engineering, clinical applications

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## Изучение потенциала применения биспецифических антител при иммунотерапии рака

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Биспецифические антитела (BsAb) – принципиально новое достижение в иммунотерапии рака. Это новый таргетный подход к удалению раковых клеток путем одновременного взаимодействия двух различных антигенов. Настоящий обзор рассматривает основы механизма действия и клинического применения BsAbs, подчеркивает их уникальные возможности воздействия на две мишени. Последнее позволяет нацеливать активность клеток иммунной системы на злокачественные клетки для усиления противоопухолевой активности. Авторы рассматривают различные типы и стратегии создания BsAb, включая их модульные структуры и инновации в области инженерии, которые повысили их эффективность и специфичность. В настоящем обзоре также представлены данные доклинических и клинических исследований, демонстрирующие многообещающие результаты и истории успеха при терапии различных типов рака. Несмотря на терапевтический потенциал, разработка BsAbs сталкивается с такими проблемами, как производственные сложности, проблемы стабильности и токсичности, которые мы рассматриваем наряду с текущими решениями, и нормативные аспекты. Объединяя последние достижения и тенденции, эта статья представляет собой исчерпывающий обзор BsAbs и их преобразующей роли в будущем терапии рака.

**Ключевые слова:** биспецифические антитела, иммунотерапия рака, двойное таргетирование, инженерия антител, клинические применения

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## Introduction

Bi-specific antibodies (BsAbs) are an innovative class of therapeutic antibodies engineered to recognize and bind to two different antigens or epitopes simultaneously. This dual-targeting capability offers a significant advantage over conventional monoclonal antibodies (MoAbs), which are monospecific and target a single antigen. The structure of BsAbs typically includes two different antigen-binding sites, which can be designed in various formats such as tandem single-chain variable fragments (scFvs), dual-variable domain immunoglobulins, or full-length IgG-like antibodies. The modularity in their design allows for a high degree of specificity and flexibility in therapeutic applications [1].

The concept of BsAbs dates back to the 1960s when Nisonoff and his team first proposed the idea of combining two different antigen-binding sites within a single antibody structure. However, it was not until the advent of hybridoma technology in the 1970s that the practical production of pure antibodies became feasible, revolutionizing the field of immunotherapy [2]. The development of quadroma technology in the 1980s further advanced BsAbs by allowing the creation of hybrid-hybridomas capable of producing antibodies with dual specificity. Significant milestones include the development of the single-chain variable fragment (scFv) technology in the late 1980s and the introduction of the "knobs-into-holes" engineering approach in the 1990s, which improved the efficiency of assembling heterodimeric antibodies [3].

Compared to MoAbs, BsAbs offer several therapeutic advantages, particularly in oncology. MoAbs typically target a single antigen, which can limit their efficacy due to the heterogeneity of tumors and the potential for antigen escape. In contrast, BsAbs can simultaneously engage two different antigens, enhancing their ability to recruit immune effector cells and target tumor cells more effectively. For example, the bispecific T-cell engager (BiTE) antibody blinatumomab links CD3 on T cells with CD19 on B cells, leading to targeted cytotoxicity against B-cell malignancies. Such dual targeting not only improves specificity but also reduces the likelihood of resistance mechanisms that often undermine single-target therapies [4].

The historical progression of BsAbs has been marked by continuous improvements in antibody engineering and production techniques. Initial challenges, such as the correct assembly of heavy and light chains, have been addressed through various innovative approaches, including the use of linker peptides and recombinant DNA technologies. These advancements have enabled the production of BsAbs with improved stability, efficacy, and safety profiles. Currently, there are several BsAbs approved for clinical use, and numerous others are undergoing clinical trials, demonstrating the broad potential of this technology in treating various cancers [5].

## Methodology

A systematic approach was utilized for this literature review, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to gather relevant articles and studies in Emergency medicine's critical cases. A thorough search was conducted in reputable databases, including PubMed, Google Scholar, Scopus, and Web of Science, using specific keywords such as "Bi-specific antibodies," "Cancer immunotherapy," "Dual-targeting," "Antibody engineering," "Clinical applications" to ensure comprehensive coverage of pertinent literature.

The inclusion criteria for the studies were as follows: (1) publications in English, (2) studies focusing specifically on cancer immunotherapy, and (3) studies reporting on bi-specific antibodies. Initially, 92 articles were retrieved from the databases. After a meticulous examination to eliminate duplicate references, 29 unique articles met the inclusion criteria. These articles underwent rigorous evaluation through a comprehensive assessment of their titles, abstracts, and full texts, confirming their alignment with the established inclusion criteria and warranting their inclusion in the review.

To provide a clear overview of the study selection process, the PRISMA flow diagram is included below (fig. 1), illustrating the number of records identified, screened, and included in the review, along with reasons for exclusion at each stage.

## Mechanisms of action

Bi-specific antibodies demonstrate a range of mechanisms of action that contribute to their efficacy in cancer immunotherapy. One of their primary capabilities is dual-targeting, which involves simultaneously binding to two different antigens. This dual-targeting approach allows BsAbs to bridge immune cells with cancer cells effectively, thereby enhancing the immune response against tumors [1]. By binding to a tumor-associated antigen (TAA) on cancer cells and a specific marker on immune cells, BsAbs can direct immune effector cells, such as T cells, to the tumor site, promoting targeted cell killing [6].

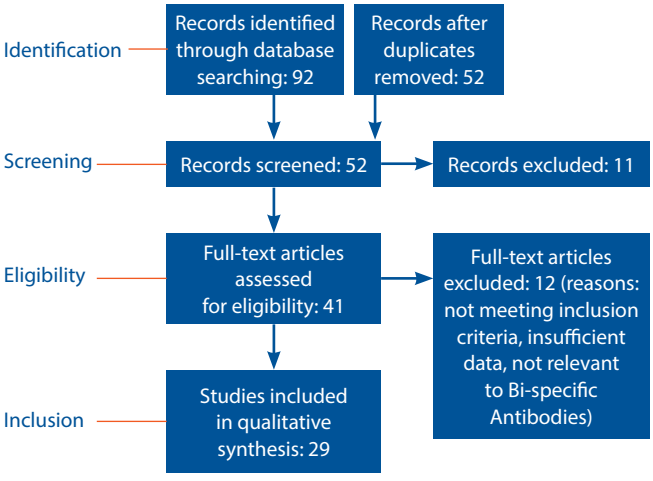


**Fig. 1.** *Illustrates the PRIMSA flow diagram*

A notable example of this is the BsAb blinatumomab, which targets CD19 on B cells and CD3 on T cells, facilitating the recruitment and activation of T cells to destroy B-cell malignancies [1]. This mechanism is not limited to T cells; BsAbs can also engage natural killer (NK) cells and macrophages through similar strategies. For instance, AFM13 targets CD30 on Hodgkin lymphoma cells and CD16A on NK cells, thereby enhancing the NK cells' cytotoxic activity against the cancer cells [6].

Moreover, BsAbs can modulate immune checkpoints, which are critical regulators of immune activation and tolerance. By targeting checkpoint molecules such as PD-1, CTLA-4, and LAG-3, BsAbs can release immune cells from inhibitory signals, thereby amplifying the anti-tumor immune response. These antibodies can be designed to block inhibitory pathways or activate stimulatory pathways on immune cells, further enhancing their anti-cancer efficacy [7].

To enhance specificity and efficacy, BsAbs are engineered with advanced molecular designs that improve their binding affinity and stability. These designs include tandem diabodies (TandAbs) and dual-variable domain immunoglobulins (DVD-Igs), which allow for more precise targeting and reduced off-target effects. Such engineering innovations help BsAbs to achieve better tumor localization and penetration, thus improving therapeutic outcomes [8].

## Types and design of Bi-specific antibodies

Bi-specific antibodies exhibit a variety of structural designs and classifications that are critical for their function in cancer immunotherapy. One common classification is based on their structure, which includes formats such as tandem single-chain variable fragments (scFvs) and dual-variable domain antibodies (DVD–Igs). Tandem scFvs are composed of two single-chain variable fragments linked together, allowing simultaneous binding to two different antigens. This format offers flexibility and reduced size, enhancing tissue penetration and reducing manufacturing complexity [9]. Dual-variable domain antibodies, on the other hand, consist of two antigen-binding sites engineered within the same molecule, providing the ability to engage two targets with high specificity [9].

Modular designs and engineering strategies are pivotal in optimizing the functionality of BsAbs. One such strategy is the "knobs-into-holes" technology, which involves engineering the antibody's Fc region to create asymmetrical interfaces that promote the heterodimerization of two different heavy chains. This method enhances the stability and manufacturability of BsAbs. Additionally, the CrossMab technology allows for the efficient swapping of antibody domains to produce bi-specific molecules with distinct antigen-binding sites, enhancing their therapeutic potential [10].

Advances in antibody engineering technologies have significantly propelled the development of BsAbs. Recent progress in computational modeling and structure-based design has enabled the precise engineering of antibody-antigen interactions, improving the binding affinity and specificity of BsAbs. Techniques such as directed evolution and high-throughput screening facilitate the rapid optimization of BsAb candidates, ensuring that only the most effective molecules advance to clinical development [11]. Furthermore, advances in protein engineering have introduced novel formats such as trispecific antibodies and multi-specific antibodies, which can target multiple antigens simultaneously, providing a more comprehensive approach to cancer treatment [1].

These innovations in BsAb design and engineering underscore the transformative potential of these molecules in oncology, offering new avenues for targeted cancer therapy with improved efficacy and reduced side effects.

## Preclinical studies and animal models

Preclinical studies have been pivotal in the development of BsAbs for cancer therapy, offering crucial insights into their efficacy and safety profiles before human clinical trials. These studies often employ various animal models to mimic human disease conditions and evaluate therapeutic responses.

Key findings from preclinical research indicate that BsAbs exhibit significant potential in targeting and eliminating cancer cells. For instance, studies using mouse models have demonstrated that BsAbs can effectively bridge T cells with cancer cells, leading to potent anti-tumor activity. The use of cell line-derived xenograft models, where human cancer cells are implanted into immunodeficient mice, has been particularly instrumental in these evaluations. Such models allow for the assessment of BsAbs in a controlled environment that closely mimics human tumor growth and metastasis [12, 13].

Animal model studies have provided valuable insights into the mechanisms by which BsAbs function and their potential therapeutic benefits. For example, genetically engineered mouse models have been used to study the dual-targeting capabilities of BsAbs, revealing how these antibodies can simultaneously bind to two different antigens, thereby enhancing specificity and reducing off-target effects. Additionally, these models have helped elucidate how BsAbs modulate immune checkpoints, further augmenting their anti-tumor efficacy [13, 14].

The safety and efficacy profiles of BsAbs have also been extensively evaluated in animal models. These studies typically involve monitoring the animals for adverse effects, such as cytokine release syndrome, and assessing the pharmacokinetics and pharmacodynamics of the BsAbs [15]. Non-human primate models, in particular, have been used to study the safety of BsAbs due to their closer physiological similarities to humans. These models help in understanding the potential immunogenicity and toxicity of BsAbs, providing a comprehensive safety assessment before clinical trials [12, 13].

## Clinical applications and trials

The clinical application of BsAbs in oncology has gained significant traction, with numerous ongoing clinical trials and several notable successes. Current

clinical trials are exploring BsAbs across various cancer types, showcasing their versatility and potential in cancer immunotherapy.

One of the most promising areas of clinical research involves BsAbs targeting CD3 and CD20, which have shown considerable efficacy in treating B-cell lymphomas. For instance, glofitamab, a BsAb with a unique 2:1 design enabling high-avidity bivalent binding to CD20 on B cells, has demonstrated impressive results. In a phase 1/2 trial for relapsed or refractory diffuse large B-cell lymphoma (DLBCL), glofitamab achieved an overall response rate (ORR) of 56 % and a complete response rate of 43 %, with a median response duration of 18.4 months [16].

Additionally, other BsAbs, such as epcoritamab and mosunetuzumab, have shown significant promise. Epcoritamab, in clinical trials, has demonstrated strong efficacy and manageable safety profiles, particularly in combination therapies. Similarly, mosunetuzumab has been evaluated in various settings, including as a monotherapy and in combination with other treatments, showing encouraging response rates and durability [1].

Clinical trials also highlight the success of BsAbs in solid tumors. For example, the phase 1 study of zanidatamab, a BsAb targeting HER2, showed durable responses in patients with advanced HER2-positive cancers, including gastroesophageal adenocarcinoma and biliary tract cancers. These findings underline the potential of BsAbs to provide new therapeutic options where traditional therapies have failed [17].

BsAbs are also being tested in combination with other therapies to enhance their efficacy and overcome resistance mechanisms. For instance, combining BsAbs with immune checkpoint inhibitors or standard chemotherapies has shown synergistic effects, potentially leading to more effective and durable responses in patients with refractory or relapsed cancers [18].

## Challenges and limitations

The development and clinical implementation of BsAbs in oncology are accompanied by several challenges and limitations. One of the primary issues is the complexity of manufacturing BsAbs, which involves intricate production processes to ensure correct folding and stability. The use of different platforms, such as mammalian and microbial expression systems, has been explored to address these complexities [19]. However, the variability in product quality and the presence of aggregates remain significant hurdles [20].

Stability and half-life are critical factors for the effectiveness of BsAbs. Engineering BsAbs to have an extended half-life while maintaining their functional integrity is a complex task. Techniques such as the introduction of Fc regions or albumin-binding domains have been employed to improve serum half-life, yet these modifications can sometimes lead to increased immunogenicity or altered pharmacokinetics.

Off-target effects and toxicity are major concerns with BsAbs. The dual-targeting nature of these antibodies increases the risk of unintended interactions with non-target tissues, leading to potential off-target toxicity. Strategies to enhance specificity, such as the incorporation of conditional activation mechanisms, are being developed to mitigate these risks. Nonetheless, achieving a balance between efficacy and safety remains a delicate process [21].

Immune-related adverse events are also a significant challenge in the clinical application of BsAbs. These antibodies can trigger an exaggerated immune response, leading to conditions such as cytokine release syndrome (CRS). Preclinical and clinical studies are focused on identifying biomarkers and developing protocols to predict and manage these adverse events effectively [21].

## Combination therapies

Combination therapies involving BsAbs represent a promising frontier in cancer treatment, enhancing the therapeutic effects of existing modalities while aiming to mitigate their limitations. BsAbs exhibit synergistic effects when combined with other immunotherapies, such as immune checkpoint inhibitors. These combinations leverage the dual-targeting capability of BsAbs, which can simultaneously engage cancer cells and immune cells, thereby amplifying the immune response against tumors. For instance, combining BsAbs with PD-1/PD-L1 inhibitors has shown potential in enhancing anti-tumor efficacy by effectively overcoming immune evasion mechanisms employed by cancer cells [22].

The integration of BsAbs with traditional treatments, including chemotherapy and radiation, also holds significant promise. Chemotherapy can increase the immunogenicity of tumors, making them more susceptible to subsequent immune-mediated attacks facilitated by BsAbs. Notably, clinical trials have demonstrated improved outcomes when BsAbs are used alongside conventional treatments. For example, the combination of pembrolizumab, an anti-PD-1 antibody, with platinum-based chemotherapy in non-small cell lung cancer has resulted in significantly improved overall survival rates compared to chemotherapy alone [23, 24].

However, the use of combination therapies is not without risks. One of the primary concerns is the potential for increased toxicity and immune-related adverse events. The dual action of BsAbs can sometimes lead to off-target effects, exacerbated by the addition of other potent therapies. Monitoring and managing these adverse effects require careful consideration and robust clinical strategies [5].

Despite these challenges, the potential benefits of combining BsAbs with other therapies are substantial. These combination strategies are at the forefront of clinical research, with numerous trials ongoing to optimize dosing regimens, minimize side effects, and maximize therapeutic efficacy. The evolving landscape of combination therapies

involving BsAbs continues to offer hope for more effective and durable cancer treatments [22, 23].

## Regulatory and approval pathways

The regulatory and approval pathways for BsAbs involve a series of rigorous steps and considerations to ensure safety and efficacy. One of the primary challenges in this process is the complexity of manufacturing and quality control. BsAbs, being more intricate than monoclonal antibodies (mAbs), require advanced technologies and methodologies for production, which can complicate scaling and consistency [25]. Regulatory bodies, such as the FDA and EMA, impose stringent guidelines to oversee these complexities, ensuring that each batch of BsAbs meets the necessary standards before approval [25].

Several BsAbs have successfully navigated these pathways, demonstrating their therapeutic potential. For instance, Epcoritamab, marketed as EPKINLY™, targets CD20 and CD3, and has been approved for treating diffuse large B-cell lymphoma. Similarly, Glofitamab, known as Columvi®, targets CD20 and CD3e, and has shown promising results in treating diffuse large B-cell lymphoma [26]. These approvals mark significant milestones, showcasing the therapeutic efficacy of BsAbs in oncology.

The regulatory success of BsAbs can be attributed to the robust preclinical and clinical data supporting their use. Case examples like Epcoritamab and Glofitamab highlight the importance of demonstrating clear clinical benefits and manageable safety profiles. Regulatory agencies consider multiple factors, including the innovative design of BsAbs, their dual-targeting capabilities, and their ability to bridge immune cells with cancer cells [17].

The approval process also involves addressing potential safety concerns, such as off-target effects and immune-related adverse events. Comprehensive clinical trials are essential to identify and mitigate these risks, ensuring that BsAbs provide more benefits than risks to patients [17].

## Future directions and innovations

The field of BsAbs is rapidly evolving, driven by emerging technologies and the potential for personalized cancer treatment. Significant advancements are being made in the design and development of BsAbs, which are increasingly seen as promising tools in the fight against cancer.

Emerging technologies in BsAb development are enhancing their specificity, efficacy, and safety. For instance, new methods in protein engineering and modular design are allowing for more precise targeting of cancer cells while minimizing off-target effects. Techniques such as site-specific conjugation and advanced screening platforms are improving the functionality and stability of BsAbs, thereby enhancing their therapeutic potential [27]. Additionally, the integration of artificial intelligence (AI) and machine learning in the design and development processes is streamlining the identification of optimal antibody configurations and target sites, leading to more effective treatments [4].

Personalized cancer treatment is another promising direction for BsAbs. Advances in genomic profiling and precision medicine are enabling the development of BsAbs tailored to individual patients' genetic and molecular profiles. This approach allows for the creation of highly specific antibodies that can target unique cancer mutations or biomarkers present in a patient's tumor, leading to more effective and personalized treatment regimens [28]. The use of comprehensive genomic databases and real-world data is further aiding in the identification of new targets and the refinement of BsAb therapies to meet the needs of diverse patient populations [28].

The integration of BsAbs with precision medicine and genomic profiling is paving the way for innovative treatment strategies. By leveraging detailed genetic information, researchers can develop BsAbs that not only target specific cancer cells but also adapt to the evolving nature of the tumor microenvironment. This adaptability is crucial for overcoming resistance mechanisms and improving long-term outcomes for patients. Moreover, the use of companion diagnostics and biomarker-based approaches is enhancing the selection of patients who are most likely to benefit from BsAb therapies, thereby maximizing therapeutic efficacy and minimizing adverse effects [27].

## Conclusion

In conclusion, BsAbs represent a groundbreaking advancement in cancer immunotherapy, offering novel mechanisms of action, such as dual-targeting capabilities and immune cell bridging, which enhance their therapeutic efficacy. Despite the challenges in manufacturing, stability, and potential toxicity, ongoing preclinical studies and clinical trials demonstrate their significant promise in treating various cancers. Innovations in antibody engineering, personalized treatment approaches, and the integration with precision medicine and genomic profiling are further propelling BsAbs towards becoming a cornerstone of future oncology therapies. As these advancements continue to evolve, BsAbs are poised to transform cancer treatment paradigms, offering more effective and tailored therapeutic options for patients.

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