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EDITORIAL

Innovative breakthroughs of monoclonal antibodies in tumor therapy: From "indiscriminate killing" to "precision guidance"

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Treating cancer has always been an extremely challenging endeavor in the field of medicine. Standard treatments including surgery, chemoradiotherapy, and targeted therapy have somewhat improved patient outcomes, but their drawbacks have become increasingly apparent. For instance, the surgical approach is unable to remove micrometastasis lesions; the non-specific targeting of chemotherapy and radiation raises the risk for severe adverse effects; and long-term success is hardly achievable through targeted therapy due to tumor heterogeneity and drug resistance. In light of this, scientists are on the track of devising safer and more accurate therapy techniques. Among these initiatives, monoclonal antibodies (mAbs) stand as a game-changing avenue in oncology, propelling development in tumor therapy in recent years. These antibodies can enhance the anti-cancer impact and drastically lower the off-target damage by precisely identifying tumor antigens. This editorial focuses on the most recent developments in monoclonal antibody therapy for tumors, including its precise mechanism of action, design technology supported by artificial intelligence (AI), and cutting-edge technologies such as double antigen T cell conjugates and antibody-drug conjugates. To offer a fresh viewpoint and approach to cancer treatment, the limitations and potential future development path of mAbs are also discussed.

Despite being the cornerstone of solid tumor treatment that allows for direct elimination of visible lesions, the surgical approach is unable to remove hidden micrometastases. In addition, the post-operative recurrence rate can reach over 60% due to the patient's body condition and the tumor location, and resection of vital organs may cause irreversible functional damage.[1] The traditional model of tumor treatment, encompassing surgery, chemotherapy/radiotherapy, and targeted therapy, is now facing the three main problems stated above. In addition to destroying cancer cells, radiotherapy's "indiscriminate attack" feature frequently results in severe side effects such as gastrointestinal toxicity and bone marrow suppression, along with drug resistance issues.[2,3] Intrinsic flaws such as single-target limitation and inadequate immune activation render dealing with tumor heterogeneity and evolutionary escape challenging, despite the fact that targeted therapies are precise approaches.[4] For instance, some mutations in the epidermal growth factor receptor (*EGFR*) gene are crucial for the

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efficacy of *EGFR*-tyrosine kinase inhibitors. When taken as a whole, these difficulties highlight the difficulty of treating cancer and underscore the need for a multifaceted, synergistic therapeutic approach that strikes a balance between accuracy, safety, and effectiveness.[5]

Bi-epitope antibody technology can target two antigenic epitopes at the same time for tumor antigen escape; for example, MCLA-128's dual inhibition of human epidermal growth factor receptor (HER)2/HER3 dramatically lowers the chance of treatment resistance.[6] Clinical trials are showing promise for immune microenvironment modulation techniques using transforming growth factor-beta inhibitors in conjunction with antibody medicines.[7]

Dual antigen T-cell engagers efficiently attract T-cell cytotoxicity to solid tumor cells by combining antigen-binding fragments that target tumors with single-chain variable fragments that target CD3. These compounds improve tumor selectivity by combining dual-targeting properties, which help the immune system target cancer cells more successfully while preserving healthy tissue. As an additional illustration, antibody-drug conjugates specifically deliver deadly medications to the tumor microenvironment. For instance, DS-8201 considerably lowers systemic toxicity by carrying eight chemotherapeutic molecules per antibody.[8] The 5-year survival rate for patients with metastatic melanoma has increased from <10% to 52% when immune checkpoint drugs, such as pembrolizumab, are used with CTLA-4 inhibitors.[9] Strategies based on aptamers have drawn interest as a substitute or addition to conventional antibody treatments. Short nucleotide sequences known as aptamers have the ability to attach to particular proteins and, in contrast to antibodies, have a reduced molecular weight, greater stability, less immunogenicity, and improved tissue absorption.[10]

The advent of AI technologies has brought significant implications for the design of antibodies. Specifically, these technologies, or tools, can aid in antibody characteristics forecast, improve their design, and accelerate development. Research has demonstrated the effectiveness of Generative Adversarial Networks in producing new antibody sequences from pre-existing datasets that have high affinity and exploitable characteristics.[11] Their smooth integration is hampered by issues such as the intricacy of antibody interactions, data sparsity, a lack of computational techniques, the repeatability and openness of AI approaches, and model generalization capabilities. To enhance the prediction potential and application possibilities of AI in mAbs development, future strategies should involve creating standardized frameworks, enhancing data quality, integrating AI with experimental techniques, and utilizing generative models.[12]

Glycosylation engineering alters the glycosylation patterns of antibodies to improve their overall pharmacological characteristics and effector activities. While improving some characteristics, the glycosylation engineering procedure must guarantee that the binding affinity to the target antigen and Fc receptor stays constant. Research has indicated that certain N-glycans on receptors, including FcγRIIIa, can have a major impact on how well they interact with antibodies.[13] The regulatory environment for therapeutic antibody glycosylation must be considered to improve therapeutic efficacy without compromising safety.

By precisely identifying tumor antigens, mAbs, such as trastuzumab for HER2-positive breast cancer and rituximab, a therapeutic medication for lymphoma that targets CD20 achieve precision strikes and minimize off-target consequences. It works by inhibiting the tumor signaling pathway directly and then triggering antibody-dependent cellular cytotoxicity mediated by natural killer cells. Comparing trastuzumab combination chemotherapy to traditional chemotherapy, clinical data indicate a 40% decrease in the incidence of cardiotoxicity.[14]

Tumor treatment has entered a new era of precision thanks to precise medication guided by corresponding diagnostic technology. For instance, trastuzumab is recommended for patients with immunohistochemically detected HER2 protein, and immunotherapy is recommended for patients with non-small cell lung cancer with high expression of PD-L1.[5] Moreover, the introduction of next-generation sequencing technology has greatly accelerated the detection of actionable mutations and variants.[15] Through circulating tumor DNA analysis, a dynamic monitoring system enables real-time modifications to treatment regimens, thereby overcoming the time lag experienced in traditional treatment. The development of platforms for local therapeutic delivery, such as Shielded and Retargeted Adenovirus, allows tumor cells to function as biofactories for the *in situ* production of antibodies, which greatly improves tumor-to-serum concentration ratios when compared to systemic administration.[16]

The effectiveness of mAbs may be influenced by their biological formulation. Drug delivery is revolutionized by subcutaneous dose forms, and solid formulations are more stable than liquid ones and may last longer on the shelf if properly reconstituted before administration.[17] Optimizing their formulation for efficient delivery is especially crucial with the advent of new biotherapeutic modalities, such as bispecific and multivalent antibodies.[18] By competitively adhering to the formulation interface, amphiphilic copolymers, for instance, lessen the possibility of protein interfacial aggregation.[19]

Monoclonal antibody use is still increasing in low- and middle-income nations and the high expense of these biologics presents a significant problem for global healthcare systems.[20] According to studies, targeting toxicity caused by variations in receptor expression between target and off-target areas can be reduced using biosimilar techniques, such as the indirect active targeting strategy.[21] On the other hand, adding biosimilars to treatment plans is more cost-effective.[22] Optimizing regulatory frameworks and streamlining development pathways – such as comparative pharmacokinetics and risk-based immunogenicity assessment – are crucial to achieving these benefits in full. These methods can increase efficiency without sacrificing the efficacy and safety of biosimilars.[23] Home care programs, ambulatory management, and treatment model optimization can also lessen the financial burden of patient health care.

A multifaceted synergistic therapeutic system is needed as cancer therapy undergoes a significant shift and the conventional approach encounters challenges. The accuracy of mAbs is manifested through their ability to selectively identify tumor antigens. Their dual channel of action is further improved by a number of cutting-edge tactics, including antibody-drug couplings and dual-antigen T-cell junctions. In general, the invention of precise medications is promoted by the inception of new diagnostic technology. Future developments in mAb development will be aided by dual epitope antibody technology, AI-powered antibody design, glycosylation engineering, etc. However, the impact of biologics and costs must be taken into account to optimize the drug delivery process, lower costs, and advance the development of cancer treatment toward the ideals of efficiency, precision, and personalization. Undeniably, the current research and application trends show that tumor treatment is ushering in a new era as a result of the emergence of precise technologies, as well as a revolution in treatment philosophy.

mAbs represent a significant impetus behind the revolution of the cancer treatment landscape. With selective targeting of tumor antigens, mAbs cause lesser adverse effects, while amplifying the therapeutic effects. The effectiveness of mAbs in cancer treatment is also strengthened by their incorporation into cutting-edge technologies. Nevertheless, wider clinical adoption of mAbs is currently restricted by tumor antigen escape and expensive production costs. Ongoing developments, however, provide encouraging solutions. For instance, the emergence of better medication delivery technologies can help with increasing their precision, while the introduction of AI can aid in accelerated antibody design. To address the problem of drug resistance, researchers are also actively investigating novel tumor antigens and multi-targeting techniques. Crucially, these advancements allow for customized treatments based on the requirements of each patient. Novel mAb designs and delivery systems will probably provide safer, more efficient cancer treatments as research advances. With all these developments coming to realization in the future, oncology care may be redefined by fusing the latest technologies and techniques with patient-specific strategies.

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