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CHEMICAL STRATEGIES FOR LINKER DESIGN IN ANTIBODY-DRUG CONJUGATES : ENHANCING STABILITY AND EFFICACY

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ABSTRACT : Antibody-Drug Conjugates (ADCs) have emerged as a promising class of cancer therapeutics, uniquely combining the specificity of monoclonal antibodies with the potency of cytotoxic drugs. Central to their success is the design of linkers that connect antibodies to drug payloads, influencing stability, drug release kinetics and specificity. This comprehensive review explores the multifaceted landscape of ADCs, categorizing linkers as cleavable and non-cleavable, elucidating factors influencing linker selection, and uncovering strategies to enhance stability while achieving precise drug release. Case studies of FDA-approved ADCs and promising candidates in development showcase linker design's transformative potential. Lessons learned from clinical trials emphasize the intricate balance between efficacy and safety. Looking forward, linker design holds the key to advancing ADC therapies, with precision linkers, innovative technologies and personalized medicine approaches promising a brighter future in the fight against cancer.

Key words : Antibody-Drug conjugates, ADCs, linker design, cleavable linkers, non-cleavable linkers, stability enhancement, targeted delivery, drug resistance, cancer therapy.

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INTRODUCTION

Antibody-Drug Conjugates (ADCs) represent a cutting-edge class of therapeutic agents in the field of oncology (Barbero *et al*, 2023). This innovative approach harnesses the specificity of monoclonal antibodies (mAbs) to selectively deliver cytotoxic drugs to tumor cells, minimizing damage to healthy tissues and maximizing therapeutic efficacy (Sievers and Senter, 2013). The development of ADCs has emerged as a promising strategy in the battle against cancer, offering new hope to patients who have exhausted conventional treatment options (Bhatt *et al*, 2023). Cancer remains one of the most formidable challenges to public health globally, with millions of lives affected each year. Conventional chemotherapy, while effective in some cases is often associated with severe side effects due to its non-specific targeting of both cancerous and healthy cells (Chari *et al*, 2014). This lack of selectivity not only compromises the patient's quality of life but also limits the maximum tolerable dose of chemotherapy drugs, thereby reducing their therapeutic potential (Breast Cancer Case Manager Branch of the Chinese Medical Education Association, 2023).

ADCs address these shortcomings by utilizing the remarkable specificity of monoclonal antibodies (mAbs) to target cancer cells with pinpoint accuracy (Cela *et al*, 2023). These mAbs are designed to recognize specific cell surface antigens overexpressed on cancer cells, allowing for precise drug delivery. Coupled with potent cytotoxic payloads, ADCs hold the promise of achieving

C. Future prospects for Linker design in ADCs

Precision linkers : Linker design will continue to evolve with a focus on achieving precise drug release at the target site. This includes the development of linker technologies that respond to specific tumor microenvironment cues (Chand *et al*, 2022).

Combination therapies : ADCs will be increasingly integrated into combination therapies with other cancer treatments, such as immunotherapies or small-molecule inhibitors. These combinations can enhance overall treatment outcomes (Sievers and Senter, 2013).

Improved payloads : Ongoing research into cytotoxic payloads aims to identify novel agents with enhanced potency and safety profiles. This will expand the range of cancers that can be effectively treated with ADCs (Bhatt *et al*, 2021).

Enhanced manufacturing : Advances in manufacturing processes will improve the scalability, reproducibility, and cost-effectiveness of ADC production, making these therapies more accessible (Bhatt *et al*, 2023).

CONCLUSION

In conclusion, this review has delved into the intricate world of Antibody-Drug Conjugates (ADCs), with a particular focus on linker design. Key findings encompassed the classification of linkers, factors influencing linker selection, strategies to enhance ADC stability, achieving targeted delivery, overcoming drug resistance, case studies of successful linker designs and lessons learned from ADC clinical trials. Emphasizing the importance of tailored linker design, we recognize that linkers serve as the critical bridge between antibodies and cytotoxic payloads, influencing stability, drug release kinetics and specificity. Looking ahead, linkers are poised to play a pivotal role in the future of ADC therapies, with the promise of precision linkers, innovative technologies, personalized medicine approaches and improved manufacturing processes, all contributing to the continued evolution of ADCs, offering renewed hope in the battle against cancer.

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