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7DC-DM1 and Beyond: Redefining Payload Delivery Strategies in Next-Generation Antibody-Drug Conjugates

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1. Abstract

Lung and colorectal cancers are among the most devastating malignancies globally, contributing to millions of cancer-related deaths each year. Despite significant advancements in targeted therapies and immunotherapies, clinical challenges continue to arise. For example, Tyrosine Kinase Inhibitors (TKIs) used for treating Epidermal Growth Factor Receptor (EGFR)-mutant lung cancer often led to acquired resistance within 9 to 14 months. Meanwhile, immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, achieve Objective Response Rates (ORR) of less than 30% in many patients. Additionally, the "don't-eat-me" signal, mediated by the CD47 signal regulatory protein α (SIRPα) axis, allows tumour cells to evade macrophage phagocytosis, further diminishing the effectiveness of existing treatments. In this context, Antibody-Drug Conjugates (ADCs) which combine the specificity of monoclonal antibodies (mAbs) with the cytotoxicity of small-molecule drugs have emerged as a transformative strategy to address these limitations. The recent study by Chiang et al. (2025) on "7DC-DM1," a non-cleavable CD47-targeting ADC, published in the International Journal of Biological Macromolecules, represents a significant advance in meeting the unmet needs of lung and colorectal cancer therapy. It offers new insights into ADC design, target engagement, and clinical translation. Furthermore, this editorial discusses potential application scenarios and future development directions for various types of ADCs.

2. Introduction

Antibody-Drug Conjugates (ADCs) have emerged as a cornerstone of precision oncology, with 15 FDA-approved agents targeting antigens like HER2, CD33, and Trop-2 [1]. Their success relies on three core components: a tumour-specific antibody, a stable linker, and a potent cytotoxic payload [2]. Yet, two longstanding barriers hinder their broader application: linker instability (cleavable linkers like valine-citrulline often release payloads prematurely, causing systemic toxicity [3] and limited tumor microenvironments (TME) modulation (most ADCs rely solely on direct cytotoxicity, failing to counteract tumour immune escape [4]. These gaps are particularly pronounced in lung and colorectal cancer leading causes of global cancer mortality [5,6], where existing targeted therapies (e.g., EGFR TKIs) induce acquired resistance within 9-14 months [7], and immunotherapies (e.g., anti-PD-1) show objective response rates < 30% [8].

CD47, a transmembrane glycoprotein overexpressed in Non-Small Cell Lung Cancer (NSCLC), colorectal cancer, and other malignancies [9-11], has emerged as a transformative ADC target. Its role as a "don't-eat-me" signal via binding to SIRPα on macrophages enables tumour immune escape [12], while its high tumour specificity makes it ideal for targeted payload delivery. Early CD47-targeted therapies, however, were limited to mAbs that only block the CD47-SIRPα axis, lacking direct cytotoxicity [13]. This limitation underscored the need for ADCs that combine CD47-mediated TME remodeling with precise payload delivery a gap filled by Chiang et al.'s development of 7DC-DM1 [14].

Chiang et al. [15]'s study (2025) is notable for its intentional reimagining of ADC payload delivery. By selecting a non-cleavable SMCC linker (instead of cleavable alternatives) and engineering two CD47-specific mAbs (7DC2 and 7DC4) that bind distinct epitopes, the researchers created ADCs (7DC2-DM1 and 7DC4-DM1) that deliver DM1 (a tubulin inhibitor) exclusively to tumor cells while activating innate immunity. This design not only addresses linker instability but also leverages epitope-specific binding to optimize efficacy and safety two critical parameters for ADC translation [15]. As we discuss below, 7DC-DM1's payload delivery strategy offers a blueprint for next-generation ADCs, where stability, specificity, and TME synergy are integrated into a single platform.

2.1. Cleavable VS. Non-Cleavable Antibody Drug Conjugates (ADCs)

Cleavable antibody-drug conjugates (ADCs) rely on the characteristics of the tumor microenvironment, such as acidic pH and a high concentration of proteases, to achieve intracellular fragmentation and release free toxins [11,14,16]. Intracellular cleavage includes pH-sensitive hydrazone bonds, glutathione-sensitive disulfide bonds, protease-sensitive peptide bonds, etc [17]. The cleavable ADC may release toxins in advance in the tumor microenvironment, producing a 'bystander effect' to kill neighboring low antigen-expressing cells [18]. The non-cleavable ADC strictly relies on the endocytosis pathway of target cells, only killing cells with high antigen expression and reducing off-target toxicity [14,19]. The cleavable type still dominates (such as CD30-MMAE ADC) [20], as the blood tumor microenvironment is more prone to trigger linker breakage. Its advantage is that the "bystander effect" of the cleavable ADC can release tumor neoantigens and enhance the response rate of immune checkpoint inhibitors. Its disadvantage is that the cleavable ADC can narrow the therapeutic window due to the early release of toxins, and thrombocytopenia is more common, as seen with Monomethyl Auristatin (MMAE) loading [18]. It also leads to drug resistance due to lysosomal escape. Non-cleavable ADCs have high cycling stability, a wider treatment window, significantly reduced bone marrow suppression risk, and reduced risk of red blood cell toxicity [19]. They also have higher targeting and internalization dependence, reducing the risk of drug resistance [14,21]. Therefore, non-cleavable CD47 targeted therapy has emerged as a low antigen-dependent target. At the same time, non-cleavable ADC preserves the function of the antibody Fc segment, enhances the synergistic effect with PD-1 inhibitors (such as promoting macrophage ADCP), etc.

2.2. Non-Cleavable Linkers: Stability as a Foundation for Safe Payload Delivery

Linker choice is the backbone of ADC payload delivery unstable linkers compromise safety, while overly rigid linkers reduce payload release in tumour cells [14]. Chiang et al.'s selection of a non-cleavable SMCC linker for 7DC-DM1 is a strategic departure from the cleavable linkers used in early CD47 ADCs [11], and it redefines how stability contributes to payload delivery precision. Key to this choice is the SMCC linker's ability to remain intact in the bloodstream, preventing off-target DM1 release. Chiang et al. demonstrated that 7DC-DM1 ADCs have an 85-90% conjugation efficiency, with minimal free DM1 detected *in vitro* evidenced by lower cytotoxicity to normal MCF-10A cells compared to free DM1 [14]. *In vivo*, this stability translated to favourable safety: in humanized C57BL/6-hSIRPα mice, 7DC4-DM1 maintained normal serum biochemical parameters (alanine transaminase, blood urea nitrogen) and did not induce thrombocytopenia or anemia a common limitation of cleavable CD47 ADCs. This contrasts with free DM1, which caused significant normal cell toxicity, highlighting the non-cleavable linker's role in confining payload activity to tumor cells.

The SMCC linker's stability also ensures payload release is tied to tumor cell internalization a critical feature for CD47-targeted ADCs. CD47 is expressed on some normal cells (e.g., erythrocytes), but 7DC-DM1's non-cleavable design means DM1 is only released when the ADC is internalized by CD47-overexpressing tumor cells. Chiang et al. confirmed this with internalization assays: 7DC-DM1 ADCs showed higher internalization efficiency in SPC-A1 (lung cancer) and MC38-hCD47 (colorectal cancer) cells than their parental mAbs, with 7DC2-DM1 exhibiting 46% internalization in MCF-10A cells. While 7DC2-DM1's stronger internalization raised concerns about off- target toxicity, 7DC4-DM1's lower internalization in normal cells balanced efficacy and safety demonstrating how non-cleavable linkers can be paired with mAb properties to refine payload delivery.

2.3. Epitope-Specific Binding: Tuning Payload Delivery for Efficacy

A second defining feature of 7DC-DM1's payload delivery strategy is its reliance on "epitope-specific CD47 binding" a factor often overlooked in ADC design but critical for targeting precision. Chiang et al.'s molecular docking simulations revealed that 7DC2 and 7DC4 bind to distinct CD47 epitopes: 7DC4 interacts with both conserved (e.g., E104, T99) and non-conserved (e.g., K39, A53) regions, overlapping with the SIRPα-binding site, while 7DC2 targets only non-conserved regions (e.g., E35, D77). This difference directly impacts payload delivery efficiency and antitumor efficacy. 7DC4-DM1's epitope binding confers two advantages for payload delivery: first, its overlap with the SIRPα site enhances TME modulation blocking the "don't-eat-me" signal while delivering DM1. In MC38 syngeneic models, this translated to extensive tumor stroma necrosis and CD11b+ immune cell infiltration, a hallmark of effective TME remodeling. Second, 7DC4's binding to conserved CD47 regions ensures cross-reactivity with human and murine CD47, enabling translation from preclinical models (e.g., MC38-hCD47 cells) to humans. In contrast, 7DC2-DM1's non-conserved epitope binding limits SIRPα blockade, reducing immune activation despite stronger internalization. This trade-off highlights how epitope selection can be used to "tune" payload delivery prioritizing either direct cytotoxicity (7DC2-DM1) or immune-cytotoxic synergy (7DC4-DM1).

Chiang et al.'s data further show that epitope binding influences ADC biodistribution a key determinant of payload delivery. In vivo Near-Infrared Fluorescence (NIRF) imaging revealed that 7DC4-DyLight680 (a fluorescent analog of 7DC4-DM1) accumulated in MC38 tumors with less off- target lung and spleen distribution than 7DC2-DyLight680. This targeted accumulation likely contributes to 7DC4-DM1's superior in vivo efficacy: in MC38-hCD47 chimeric models, 7DC4-DM1 induced complete tumor regression after two doses, while 7DC2-DM1 showed equivalent efficacy only at higher doses. By linking epitope binding to biodistribution and efficacy, 7DC-DM1 demonstrates how ADC payload delivery can be optimized at the molecular level an approach that could be applied to other targets (e.g., HER2, EGFR) to reduce off-target effects.

2.4. Dual Mechanism-of-Action: Merging Payload Delivery with TME Activation

The most innovative aspect of 7DC-DM1's payload delivery strategy is its integration of "direct cytotoxicity and immune activation" a paradigm shifts from traditional ADCs that rely solely on payload-induced cell death. By targeting CD47, 7DC-DM1 delivers DM1 to tumor cells while disrupting the CD47-SIRPα axis, creating a "feed- forward" loop: DM1-induced tumor cell death releases antigens, which are phagocytosed by activated macrophages (due to SIRPα blockade), triggering adaptive immunity. This dual mechanism amplifies payload efficacy beyond direct cytotoxicity.

Chiang et al.'s immunofluorescence staining data illustrate this synergy: in 7DC4-DM1-treated tumors, CD11b+ immune cells (macrophages, dendritic cells) infiltrated non-perivascular regions, unlike in DM1 or PBS groups, where immune cells localized to blood vessels (likely Tumor-Associated Macrophages [TAMs] that promote tumor growth). Additionally, 7DC4-DM1 reduced intratumoral microvessels (via CD31 staining), further remodeling the TME to limit tumor progression. This contrasts with 7DC mAbs (7DC2, 7DC4), which only induced modest immune infiltration without significant tumor regression proving that payload delivery, when paired with TME activation, is far more effective than either mechanism alone.

This dual approach also addresses a key limitation of ADCs: resistance to payloads. By activating immunity, 7DC-DM1 may prevent the emergence of DM1-resistant clones an issue that plagues single-mechanism ADCs [15]. While did not explore long-term resistance, their data suggest that 7DC4-DM1's ability to remodel the TME could extend its clinical utility a hypothesis that warrants further investigation.

3. Clinical Translation and Future Direction of ADCs

There are challenges in the field of translational medicine, such as the high expression of CD47 in solid tumors, such as triple negative breast cancer (TNBC positive rate over 70%), which is associated with poor prognosis (HR=2.3) [22]. However, the linear relationship between its expression level and the efficacy of anti-CD47 therapy is not clear yet, and some patients have high CD47 expression but ineffective treatment. Due to the polymorphism of SIRPα, this condition can affect the affinity with CD47, leading to 20% of patients developing drug resistance, which needs to be reversed by combining SIRPα inhibitors (such as ALX148) [23]. Considering blood toxicity, we tend to use IgG4 subtype antibodies (such as Magrolimab) [24] or glycosylation optimization (such as AK117) to reduce the risk of hemolysis, and the incidence of grade 3 anemia can be reduced to 5%. In the future, targeted delivery systems (such as ferritin carriers) need to be developed to enhance the local effect of tumors, and SIRPα silencing technology in CAR-M cells needs to be explored (with a 40% increase in complete response rate) [25].

By simultaneously blocking CD47-SIRPα (relieving macrophage suppression) and PD-1/PD-L1 (activating T cells), dual activation of innate and adaptive immunity is achieved. For example, IMM2520 shows synergistic anti-tumor effects in animal models and enhances macrophage phagocytic activity through IgG1 Fc [26]. Compared with dual-target therapy, the CD47 monoclonal antibody is prone to blood toxicity (such as anemia), while the PD-1 monoclonal antibody has limited efficacy in "cold tumors" [11, 14, 16]. Bispecific antibodies enhance safety by reducing off-target toxicity, such as selective binding of IBI322 to tumor cell CD47 [27, 28]. In the treatment of solid tumors, it is necessary to overcome the immunosuppressive microenvironment; however, CD47/PD-L1 bispecific antibodies can synergistically enhance macrophage infiltration (such as IMM2520) and T cell activation. In the treatment of blood cancer, CD47 monoclonal antibodies (such as Magrolimab) can directly target blood cancer cells with high expression of CD47, but the Fc segment needs to be optimized to reduce red blood cell toxicity. In a solid tumor breakthrough, PD-1/IL-2 bispecific antibody (IBI363) achieved a median OS of 16.1 months in MSS type colorectal cancer (traditional immune resistant), significantly better than historical data (6.4-9.3 months) [29]. In the development of tertiary antibodies, such as CD3/BCMA/GPRC5D tertiary antibodies, Johnson & Johnson's JNJ-79635322 has shown deep remission in myeloma, but the incidence of Cytokine Release Syndrome (CRS) needs to be optimized.

Bispecific antibody ADCs, such as EGFR/HER3 bispecific antibody-related ADCs (BL-B01D1), are currently beginning to be gradually developed [30]. In EGFR mutant NSCLC treated with such ADCs, the Objective Response Rate (ORR) reaches 63.2% and is effective against rare mutations such as exon 20 insertion [31]. It may become a new paradigm for cross-tumor therapy.

4. Conclusion

In the era of ADC3.0, the scenario of precise release technology and combination therapy is very clear. In future development, firstly, dual target ADCs such as CLDN18.2/CD47 dual antibody ADC (PT886) will be developed to overcome solid tumor heterogeneity [32, 33]. Secondly, targeting tumor extracellular matrix proteins (such as fibronectin) breaks through the limitations of traditional ADC internalization. Finally, develop novel DNA-damaging agents, such as Pyrrolobenzodiazepines (PBD) dimers [34], to enhance the killing efficacy of non-cleavable ADCs.

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