Advancing ADC Therapeutics with Next-generation Site-Specific Glycan Conjugation and Dual-Payload Flexibility

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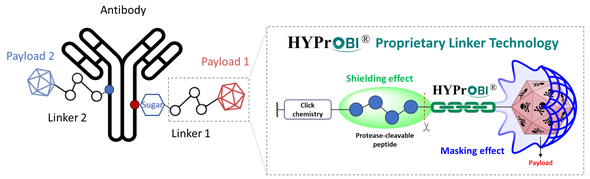
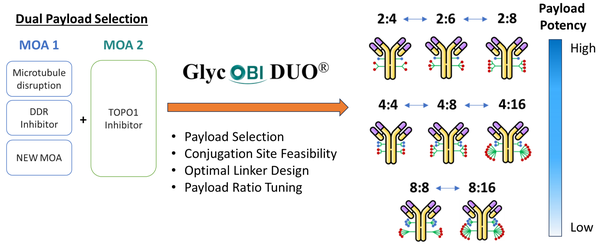
The Features of GlycOBI DUO® ADCs

- **GlycOBI DUO®** technology, a **dual-payload platform**, enables site-specific enzymatic conjugation ADCs carrying two distinct payloads.
- **HYPrOBI®** novel linker technology:
  - ➢ **Masking effect:** Hydrophobicity masking of payload to **enhance stability and anti-tumor activity**
  - ➢ **Shielding effect:** Protecting environment to **reduce premature payload releasing into circulation** before targeting to tumor cell and control releasing kinetics of payload



Dual-Payload ADCs with Precisely Controlled DAR Ratios to Overcome Tumor Resistance and Improve Tolerability



- **Site-Specific Precision:** Well-defined dual conjugation sites for superior ADC stability and homogeneity.
- **Tunable DAR:** Supports high-DAR dual-payload designs with flexible ratios for tailored pharmacology.
- **Scalable Manufacturing:** Manufacturing processes can be practical, scalable, and efficient to support development.

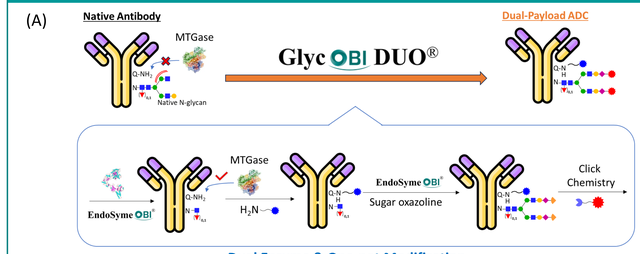
Table 1. Characterization for GlycOBI DUO® ADCs

Study type	Sample	Purity	DAR	
		Monomer (%)	MMAE	Exatecan
Conjugation site study:	**Q295**-GlcA-2MMAE + **Cys**-GGVA-8 Exatecan	97.58	1.91	8.00
Q295 vs N297 vs Cys	**N297**-GlcA-2MMAE + **Cys**-GGVA-8 Exatecan	97.01	1.92	7.94
	Q295-GlcA-2MMAE + **N297**-GGVA-8 Exatecan	98.10	1.91	7.84
DAR ratio study:	Q295-GlcA-**2MMAE** + N297-GGVA-**4 Exatecan**	97.91	1.91	3.81
2:4 vs 2:8	Q295-GlcA-**2MMAE** + N297-GGVA-**8 Exatecan**	98.10	1.91	7.84
Releasing mechanism	Q295-**GlcA**-2MMAE + N297-**GGVA**-8Exatecan	98.10	1.91	7.84
study:	Q295-**GGVC**-2MMAE + N297-**GGVA**-8Exatecan	98.22	1.92	7.88
GlcA vs GGVC	Q295-**GlcA**-2MMAE + N297-**GlcA**-8Exatecan	97.98	1.88	7.71
Modality: Mono-specific	**cMET Ab** (Q295-GlcA-2MMAE + N297-GGVA-8 Exatecan)	98.10	1.91	7.84
vs bi-specific	**OBI-221** (Q295-GlcA-2MMAE + N297-GGVA-8 Exatecan)	95.68	1.85	7.62
Mono-payload ADCs	**Q295**-GlcA-2MMAE	97.22	1.91	-
	N297-GlcA-2MMAE	97.22	1.92	-
	Q295-**GGVC**-2MMAE	96.96	1.92	-
	Cys-GGVA-8 Exatecan	97.71	-	8.00
	N297-GGVA-8Exatecan	98.29	-	7.83
	N297-GGVA-**4Exatecan**	98.22	-	3.94
	N297-**GlcA**-8Exatecan	98.46	-	7.80

Note: 1. All the materials were using cMET Ab.
2. Benchmark AZD9592 (Tilatamig samrotecan, developed by AstraZeneca) and ABBV-399 (Telisotuzumab vedotin, developed by AbbVie) were purchased from MCE.

DAR: Drug-Antibody-Ratio

Figure 1. Dual-Enzyme Strategy for Optimizing Conjugation Sites in GlycOBI DUO® ADCs



Sample name	T onset (°C)	Tm1 (°C)	Tm2 (°C)	Tm3 (°C)
cMET Ab-**Q295**-2MMAE-**N297**-8Exatecan	54.79	61.00	77.96	81.52
cMET Ab-**Q295**-2MMAE-**Cys**-8Exatecan	45.64	54.27	78.52	81.45
cMET Ab-**N297**-2MMAE-**Cys**-8Exatecan	48.03	55.37	78.31	81.48

Figure 1. Biophysical Characterization of GlycOBI DUO® ADC with Feasible Conjugation Sites. (A) GlycOBI DUO® technology enables dual enzyme and one-pot modification through Q295/N297 conjugation sites for dual-payload ADCs. (B) Reduced RPLC analysis shows consistent and precise DAR profiles across multiple conjugation site configurations. (C) DSC demonstrates that Fc site-specific conjugation preserves thermal stability better than cysteine-based conjugation, supporting Q295/N297 as optimal sites for dual-payload ADC design.

RPLC: Reverse Phase Liquid Chromatography
DSC: Differential scanning calorimetry

Figure 2. Optimized Releasing Mechanism of GlycOBI DUO® ADCs to Improve the Serum Stability

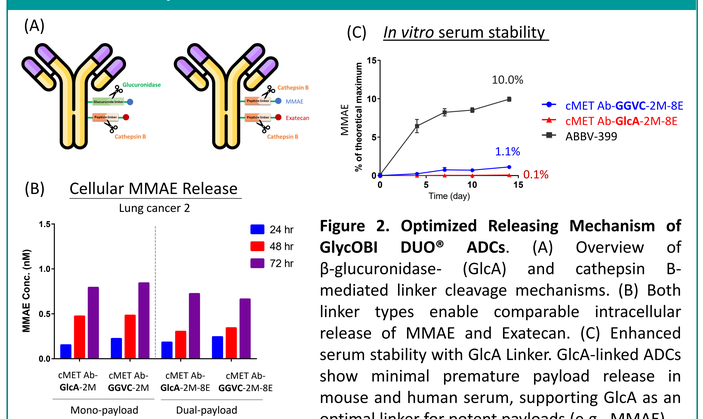
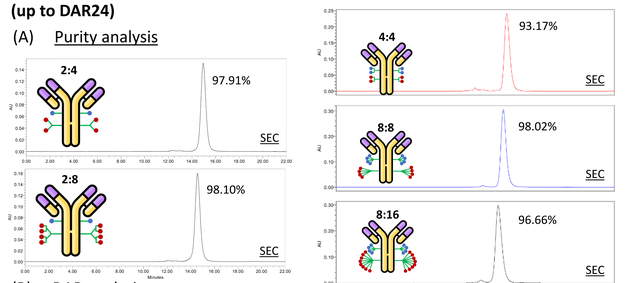


Figure 2. Optimized Releasing Mechanism of GlycOBI DUO® ADCs. (A) Overview of β-glucuronidase- (GlcA) and cathepsin B-mediated linker cleavage mechanisms. (B) Both linker types enable comparable intracellular release of MMAE and Exatecan. (C) Enhanced serum stability with GlcA Linker. GlcA-linked ADCs show minimal premature payload release in mouse and human serum, supporting GlcA as an optimal linker for potent payloads (e.g., MMAE).

Figure 3. Precise and Tunable DAR with High Purity in GlycOBI DUO® ADCs

GlycOBI DUO® Supports High-DAR Dual-Payload Designs with Flexible Payload Ratios (up to DAR24)



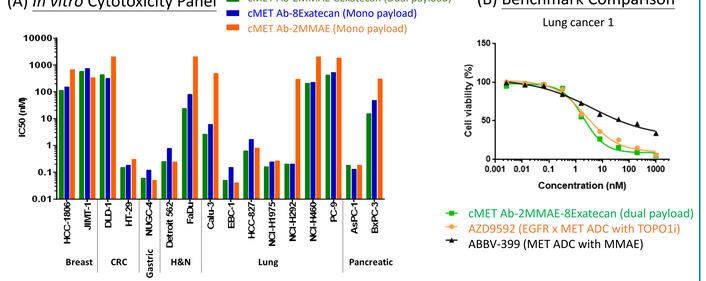
(B) DAR analysis

Payload Ratio	DAR	
	MMAE	Exatecan
2:4	1.91	3.81
2:8	1.91	7.84

Payload Ratio	DAR	
	Exatecan	DDR inhibitor
4:4	3.39	3.47
8:8	8.00	7.72
8:16	8.00	15.47

Figure 3. GlycOBI DUO® Platform Enables Precisely Controlled Payload Ratio without Aggregation. (A) SEC analysis demonstrates high purity and lack of aggregation even at high DARs. (B) DAR analysis confirm precise DAR control across different payload ratios.

Figure 4. GlycOBI DUO® ADCs Demonstrate Promising Antitumor Activity than Mono-payload ADCs and Superior to Combination



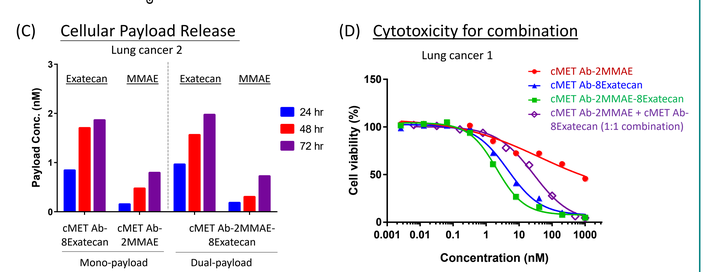


Figure 4. Broad and Potent Antitumor Activity of GlycOBI DUO® ADCs. (A) In vitro cytotoxicity panel across multiple cancer type. (B) GlycOBI DUO® ADCs ADCs show enhanced potency relative to mono-payload benchmarks using the same antibody. (C) LC-MS/MS analysis shows efficient intracellular release of each payload, comparable to their respective mono-payload ADCs. (D) GlycOBI DUO® ADCs consistently outperform mono-payload ADCs and combinations of two single-payload ADCs.

Figure 5. Bispecific GlycOBI DUO® ADCs Enable Precise and Enhanced Payload Delivery to Tumors

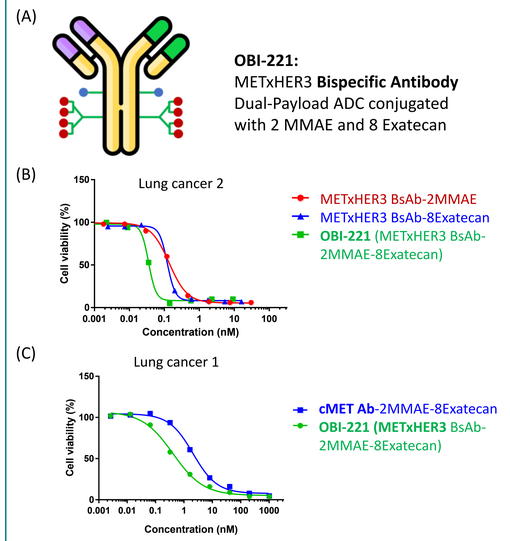
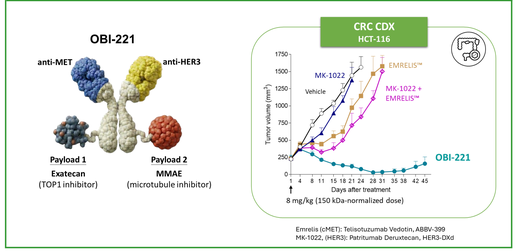


Figure 5. GlycOBI DUO® Enables Dual-Payload Conjugation Across Antibody Modalities. (A) Schematic illustration of GlycOBI DUO® platform applied to a bispecific antibody. (B & C) In vitro cytotoxicity assays show enhanced potency of the bispecific dual-payload ADC compared with mono-payload or monospecific formats.

OBI-221: An Optimal MET x HER3 Dual-payload ADC using GlycOBI DUO® Technology May Eliminate Tumor Escape Mechanisms (AACR 2026 #2665)



Summary

- GlycOBI DUO® platform offers exceptional flexibility, supporting multiple conjugation sites, tunable DAR configurations, and broad antibody modalities.
- A comprehensive linker-screening workflow ensures optimal stability, release kinetics, and payload performance for advanced ADC design.
- GlycOBI DUO® ADC demonstrated superior antitumor efficacy compared with the combination of two single-payload ADCs, highlighting its potential to enhance therapeutic outcomes.