Development of a Novel Site-Specific ADC Glycan Platform With Potential for Improved In vivo Efficacy and Stability of the ADC in Animal Studies

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Introduction

Antibody-drug conjugates (ADCs) represent a promising modality for delivering cytotoxic drugs to targeted tumor cells while avoiding off-tumor toxicities. Despite the successes in the past 20 years, development of effective ADCs with broad therapeutic window remains challenging due to the complexity of conjugation technologies and the instability of the linkers. Most platforms currently in the market as well as under clinical development may face limitations ascribed to the heterogeneity of ADCs with various drug-to-antibody ratio (DAR). This likely resulted from random conjugation and poor overall biophysical characteristics caused by linker hydrophobicity. The limitations may impact the efficacy, safety, bioavailability, and the robustness of manufacturing process of these therapeutic agents.

GlycOBI™ ADC Platform

We developed a non-genetic, engineering-free approach to generate site-specific homogenous ADCs. This was achieved by utilizing OBI proprietary enzymatic technology (EndoSymeOBI™), followed by the click chemistry to conjugate the hydrophilic linker-payload via the glycan site that naturally occurs on the antibody's Fc region. The conjugation process avoids disrupting the antibody structure, ensuring the related ADC has similar biophysical characteristics compared to native antibody. Furthermore, OBI linker technology improves the conjugation efficiency of the payload, as well as reduces the aggregation propensity, and expands the half-life of the ADC products.

The Features of GlycOBI™ ADCs:

- A site-specific conjugation platform
- Plug and Play format and compatible with any antibodies, linkers, and payloads in DAR2, DAR4, DAR6 and DAR8.
- Efficient and scalable process to generate homogenous ADCs.
- Overcomes the limitations of traditional ADCs, resulting in the improvement of efficacy and stability.

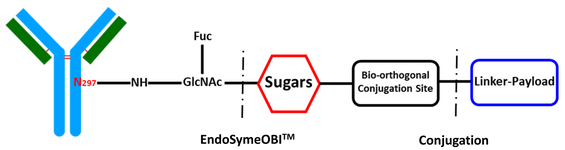


Figure 1. The major components of GlycOBI™ ADCs. The GlycOBI™ platform incorporates antibody glycan engineering technology featuring a proprietary EndoSymeOBI™ and a novel linker-payload technology.

GlycOBI™ EndoSymeOBI™

OBI Pharma

For more information of GlycOBI™, contact Kevin Poulos: kpoulos@obipharmausa.com

Antibody Glycan Engineering Technology

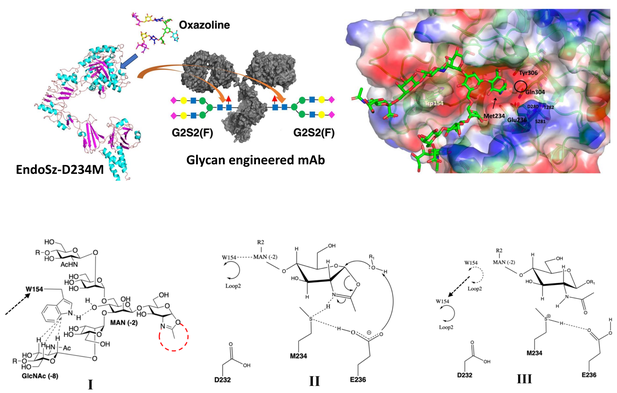


Figure 2. EndoSymeOBI™, a novel ENGase, applied in GlycOBI™ ADC platform. Transglycosylation catalyzed by EndoSz-D234M. The critical catalytic residues in the active site are numbered. The hydrogen bonds are presented as straight dashed lines. The mutagenesis study of the two key residues, Glu236 and Trp154, in relative transglycosylation activities. D232 is an important residue in deglycosylation but not in transglycosylation mechanism. The manuscript of EndoSymeOBI™ have been accepted by JACS Au. G2S2(F), Di-sialylated, bi-antennary complex-type N-glycan.

Novel Linker Technology: The Advantages of Hydra-PAB

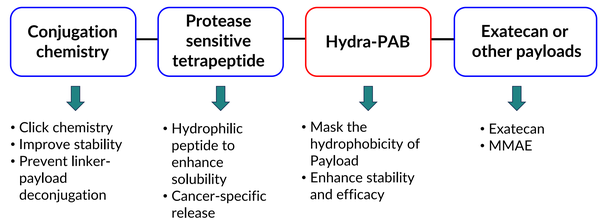


Figure 3. The strategy of linker design. GlycOBI™ utilizes a novel Hydra-PAB linker technology which creates a hydrophilic environment-to protect the linker from cleavage before targeting the tumor. The overall design of this platform provides improved stability, solubility, efficacy, and flexibility for payload selections. PAB: p-aminobenzyl

GlycOBI™ ADC – An ADC by Design

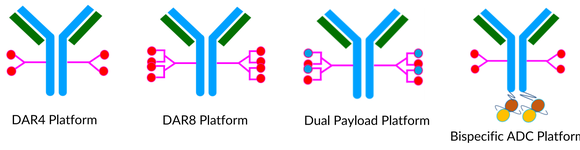


Figure 4. The different modalities of GlycOBI™ ADC platforms.

OBI-902 Anti-TROP2 GlycOBI™ ADC

OBI-902 is the next generation TROP2-directed ADC. OBI-902 is created by OBI's proprietary platform GlycOBI™. OBI-902 is currently at preclinical stage. Preliminary data of OBI-902 indicate that GlycOBI™ is an efficient platform to generate homogeneous ADCs with good stability and antitumor activity.

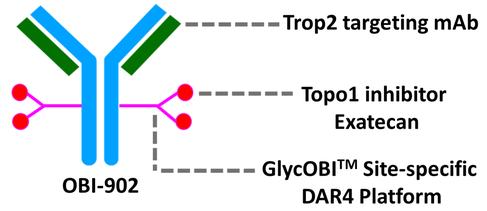


Figure 5. The design of OBI-902 GlycOBI™ ADC.

Preclinical In vitro And In vivo Proof-of-concept

1. OBI-902 GlycOBI™ DAR4 ADC Exhibits A Highly Homogeneous Nature

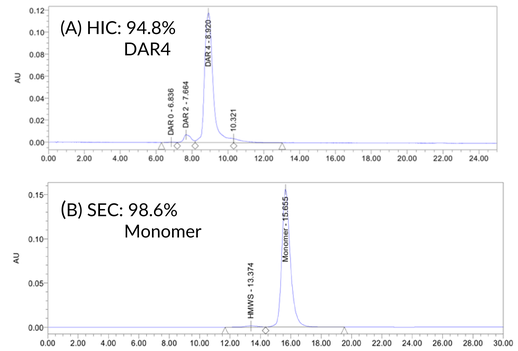


Figure 6. HIC and SEC profile of OBI-902 GlycOBI™ DAR4 ADC (A) HIC analysis: DAR0=0.42%; DAR2=4.74%; DAR4=94.8%. (B) SEC analysis: HMWS=1.36%; Monomer=98.64%.

2. Better Serum Stability of OBI-902 GlycOBI™ ADC

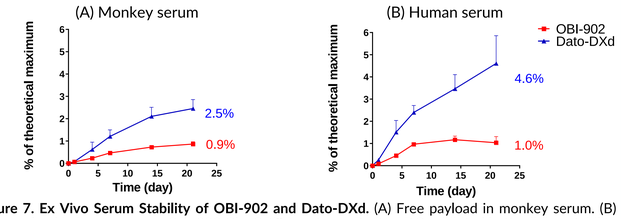


Figure 7. Ex Vivo Serum Stability of OBI-902 and Dato-DXd. (A) Free payload in monkey serum. (B) Free payload in human serum. OBI-902 GlycOBI™ exatecan DAR4 ADC exhibited better linker stability than the benchmark Dato-DXd. (Dato-DXd, datopotamab deruxtecan)

3. OBI-902 GlycOBI™ ADC Potentially Reduces the Fc-Mediated Off-Target Toxicity

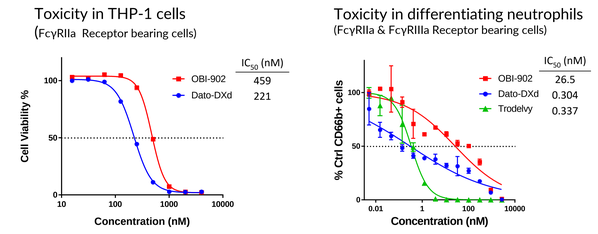


Figure 8. Off-Target Toxicity Evaluation of OBI-902 GlycOBI™ Exatecan DAR4 ADC and Dato-DXd. Dato-DXd, datopotamab deruxtecan; Trodelvy, sacituzumab govitecan; IC50, half-maximal inhibitory concentration; THP-1 cell, a human monocytic cell line derived from an acute monocytic leukemia patient.

4. Better PK Profiles of GlycOBI™ ADC in Rats

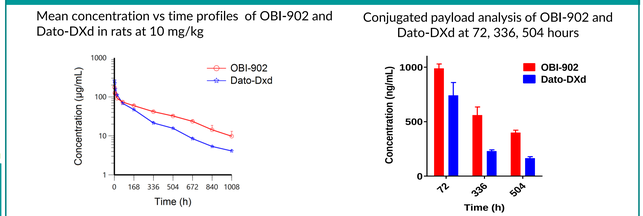
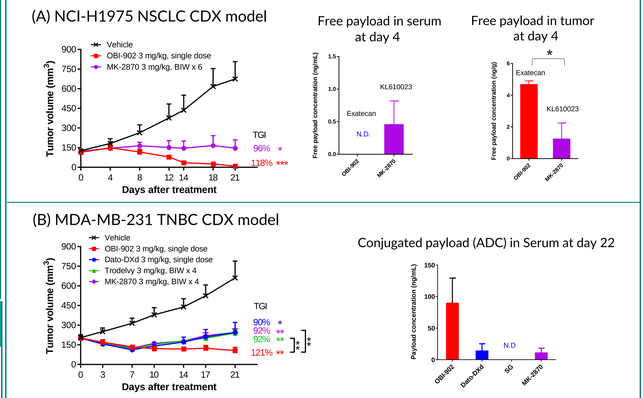


Figure 9. In vivo pharmacokinetics study of OBI-902 and Dato-DXd. OBI-902 demonstrated a favorable PK profile, with higher conjugated payload at terminal phase compared with Dato-DXd.

5. OBI-902 GlycOBI™ ADC Exhibited Better and Prolonged Antitumor Activity Than Trodelvy, Dato-DXd, and MK-2870 in Multiple CDX Models



TGI was calculated for each drug as a measure of antitumor activity. *p < 0.05; **p < 0.01; ***p < 0.001 relative to vehicle control treatment. CDX, cell line–derived xenografts; Dato-DXd, datopotamab deruxtecan; Trodelvy, sacituzumab govitecan; MK-2870 previously known as SKB264 developed by Merck and Kelun; KL610023 is the payload used in MK-2870; TGI, tumor growth inhibition; BIW: twice weekly; N.D.: not detectable at LLOQ=0.05 ng/mL

Summary

- GlycOBI™ platform is a distinct site-specific ADC platform that incorporates proprietary enzymatic glycan engineering technology and a novel linker-payload technology.
- GlycOBI™ platform can improve the stability and enhance the efficacy of ADCs.
- Different modalities of ADCs can be generated by GlycOBI™ platform, including DAR4, DAR8, dual-payload, and bispecific ADCs.
- OBI-902, a GlycOBI™ exatecan DAR4 ADC, is in preclinical stage, and has great potential to be a best-in-class TROP2 ADC.

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