Next Generation Antibody Drug Conjugates Targeting HER2 and TROP2:

Multi-Payload Conjugates™ targeting multiple mechanisms of cell killing

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Poster 2887

Introducing the CysTyr™ Platform

Current Antibody-Drug Conjugates (ADCs), though tremendously successful, leave significant residual unmet need. Trastuzumab deruxtecan (**T-DXd**), shows a CR rate of only 15.8% and 6% in HER2 high and HER2 low BC respectively.[1] Meanwhile, Sacituzumab govitecan (**SG**) shows a CR rate of only 4% in TNBC[2] and datopotomab deruxtecan (**Dato-DXd**) has a reported CR rate of 0.5% in HR+/HER2- BC. Efficacy is believed to be limited by tumor heterogeneity and eventual resistance to ADCs with sing payloads. Dual-payload ADCs have the potential to overcome this efficacy barrier.

CatenaBio has developed novel, highly stable, dual-payload targeted combination therapies, Multi-Payload Conjugates (**MPCs™**), with tunable payload ratios. Our selective conjugation platform allows the attachment of distinct payloads targeting different mechanisms of action at three unique sites on antibody scaffolds.

Here we show Catena's dual-payload MPCs targeting HER2 or TROP2 (**CATB-101**) show superior inhibition and excellent tolerability in various mouse xenograft models including models recalcitrant to topoisomerase treatment. In head-to-head comparisons Catena's **MPCs out-perform currently approved ADCs T-DXd, SG, and Dato-DXd,** demonstrating tumor elimination at low mg/kg doses across a variety of tumor models.

These results support that Catena's MPCs™ offer the potential to circumvent tumor resistance pathways to deliver deeper and more durable patient responses.

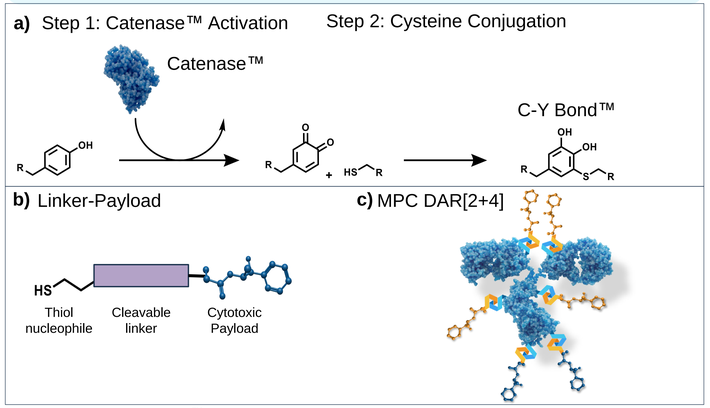

Figure 1: a) Catenase™ reaction scheme. b) Representative structure of payload-linker. c) Representative structure of CatenaBio's MPC™ DAR[2+4].

Methods

Antibodies were modified in a 2-step reaction: combining antibody and 1st payload with Catenase™ enzyme for an initial one-pot conjugation, followed by unreacted payload removal before conjugation with the 2nd payload. Payloads coupled with high efficiency to tyrosine residues on the heavy or light chains (ex. Figure 1c) and tested in vitro against cell lines of interest.

ADC samples were incubated with cultured cells for 5 days before evaluation via Alamar Blue cell viability assay. Head-to-head trials against **T-DXd, SG** and **Dato-DXd** demonstrate Catena's HER2 and TROP2 targeted MPCs significantly increased total inhibition vs standard of care (Figure 2).

Murine models using the JIMT1 (HER2^{low}) or NCI-N87 (TROP2^{high}) cell lines were dosed with either MPC™ or the ADC of choice at the listed relative dosage after tumors reached 100 mm^3 (Figure 3). Tumor elimination was observed in Catena MPC DAR[2+4].

MPCs highly potent across multiple in vitro models

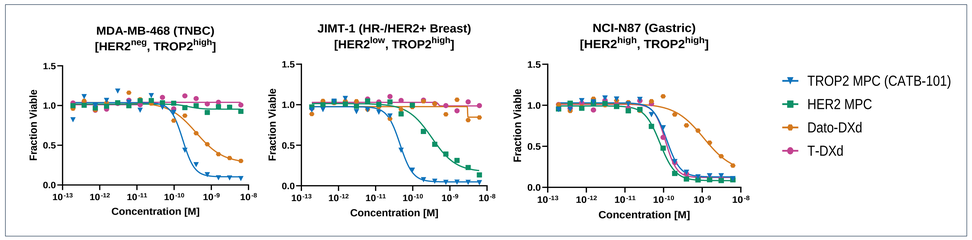

Figure 2: Comparison of Catena's dual-payload MPCs to T-DXd and Dato-DXd in vitro. TROP2 targeting (CATB-101) and HER2 targeting MPCs combining Tubulin and Topo1 inhibitors were evaluated through an in vitro activity assay on MDA-MB-468 (TNBC), JIMT-1 (HR-/HER2+ BC), and NCI-87 (GC) cell lines. Results confirm that Catena's MPCs out-perform current leading ADCs, and that JIMT-1 cells show limited sensitivity to Topo1 inhibition.

MPCs outperform top ADCs in JIMT-1 CDX mouse Models

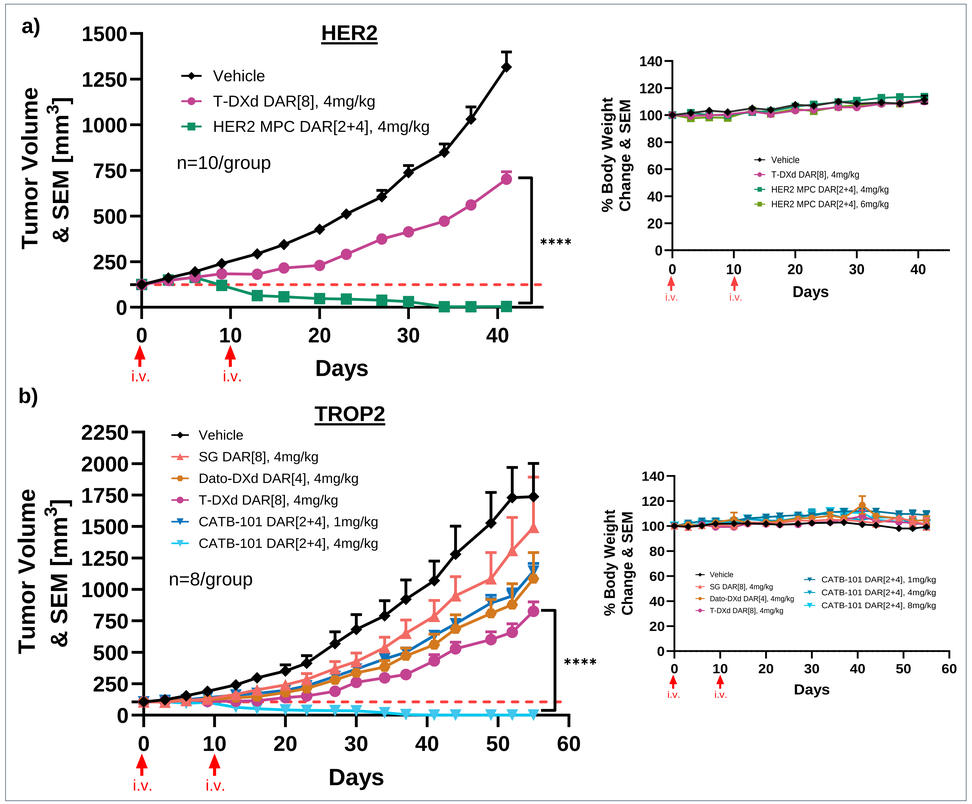

Figure 3: Comparison of Catena's MPCs to various ADCs in JIMT-1 CDX models. For all studies, mice were treated on days 0 and 10 via tail vein injection. a) JIMT-1 xenograft mice were treated with two doses of either HER2 MPC (pink) or T-DXd (green), n=10 per group. The HER2 MPC demonstrates tumor elimination at 4 mg/kg with no deviation in bodyweight observed b) JIMT-1 xenograft models comparing CATB-101 to T-DXd, Dato-DXd, or SG (n=8 per group). T-DXd shows rapid tumor growth with DAR=8 of the DXd Topo1 inhibitor, in contrast CATB-101 shows full tumor elimination with DAR=2+4, combining tubulin and Topo1 inhibitors, and no deviation in bodyweight up to 8 mg/kg

CATB-101 Rescues SG Relapsed NCI-N87 Model

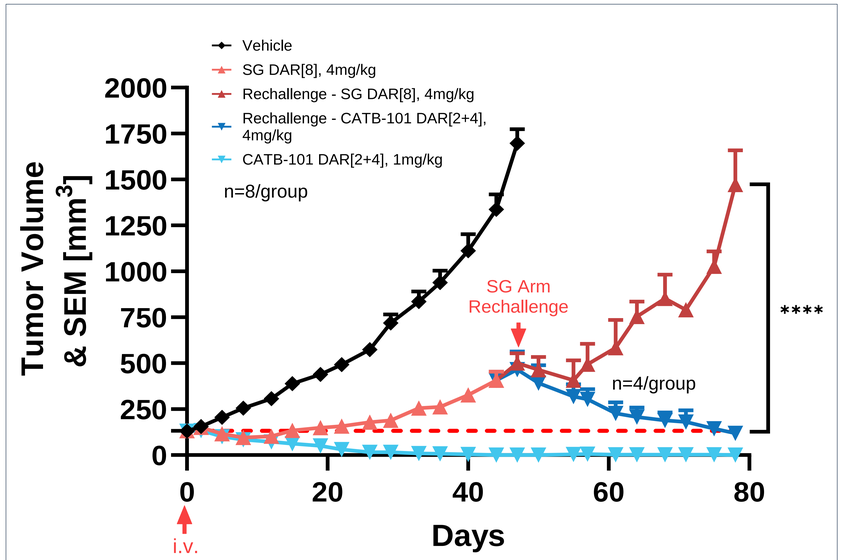

Figure 4: Comparison of CATB-101 to SG in NCI-N87 CDX model with additional evaluation of CATB-101 activity post SG treatment. Mice were treated with a single dose of either CATB-101 or SG at the doses listed above (n=8 per group). After observing progression in the SG treatment arm, the group was randomly divided into two groups (n=4 each) and re-treated with 4mg/kg of either SG, or CATB-101. SG re-treated mice exhibited rapid tumor growth and high mortality, while CATB-101 treated mice demonstrated significant tumor regression.

Conclusions

MPCs show strong activity in a variety of models, including the Top1i recalcitrant JIMT-1 tumor line, demonstrating the potential to overcome tumor heterogeneity and resistance.

- Dual-payload MPCs™ tested in vivo and in vitro across multiple cell lines showed significantly improved efficacy versus leading approved ADCs
- CATB-101 demonstrates tumor elimination at extremely low doses in NCI-N87 tumor models
- CATB-101 rescues mice that progress after SG treatment
- All studies to date demonstrate excellent tolerability as demonstrated by stable bodyweight across dosing levels
- MPCs™ show significant efficacy across a variety of antibodies and tumor types, demonstrating the versatility of the CyTyr™ platform

Next Steps

- Gram-scale production of CATB-101 complete, multi-gram scale production underway
- Advanced NHP PK and toxicology studies in progress
- PDX models of TNBC underway
- IND filing for CATB-101

References:

[1]DESTINY-BREAST-03 Trial, DESTINY-BREAST-04 Trial

[2]Bardia, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;384(16):1529-1541

[3] TROPION-Breast01 Trial