Preclinical development of YL205, a novel NaPi2b-targeting antibody-drug conjugate (ADC) with novel topoisomerase I inhibitor-based linker-payload for treatment of solid tumors

Liang Xiao[1], Wei Lian[1], Qigang Liu[1], Qing Zong[1], Shuai Song[1], Sasha Stann[2], Jiaqiang Cai[1], Tongtong Xue[1]

[1]MediLink Therapeutics(Suzhou) Co., Ltd., Suzhou, China, [2]MediLink Therapeutics USA, INC., Cambridge, MA, USA

MediLink Therapeutics

Abstract#1894

Introduction

NaPi2b, encoded by the SLC34A2 gene, is a cell surface sodium-dependent phosphate transporter that is highly expressed in certain cancers, including ovarian, lung, thyroid, and breast cancers, with limited expression in normal tissues[1-3].

YL205 is a novel NaPi2b-targeting antibody-drug conjugate (ADC), built on MediLink's tumor microenvironment activable linker-payload (TMALIN®) platform. YL205 is comprised of an anti-NaPi2b human monoclonal antibody conjugated with novel topoisomerase 1 inhibitor *via* a protease-cleavable linker at a drug-antibody ratio (DAR) of 8.

YL205 exhibited efficient internalization and potent cytotoxicity in tumor cells expressing NaPi2b. *In vivo*, YL205 was well-tolerated and effectively suppressed the growth of xenograft tumors in a dose-dependent manner. Additionally, YL205 showed a favorable PK profile and stayed highly stable in circulation, evidenced by the overlapping of ADC and total antibody PK curves in cynomolgus monkey. These results demonstrate that YL205 has favorable therapeutic margin and has the potential to address unmet medical needs in patients with NaPi2b-expressing tumors.

Here we present detailed in vitro and *in vivo* data to illustrate the preclinical features of YL205.

Structure of YL205

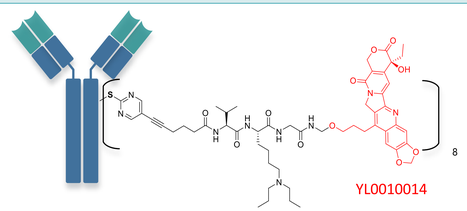


Figure 1. YL205 consists of anti-NaPi2b antibody component and drug component, linked *via* a novel tripeptide linker. The drug component ("YL0010014" hereafter) is a topoisomerase I inhibitor. The drug-antibody ratio (DAR) is 8.

YL205 Has Homogeneous DAR of 8

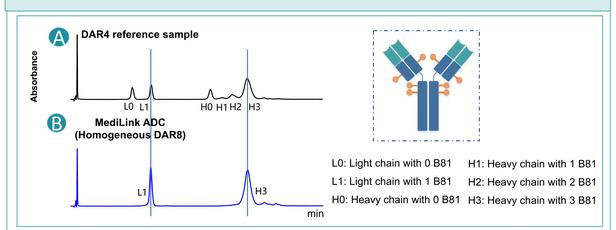


Figure 2. RP-HPLC chromatogram of reference sample (A, average DAR=4) and YL205 (B). Only L1 and H3 were detected, showing the conjugate is highly homogeneous with DAR value of 8 (B).

Binding Specificity

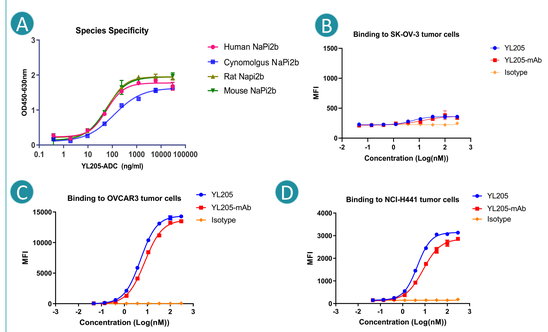


Figure 3. YL205 is capable of binding human, cynomolgus monkey, rat and mouse NaPi2b (A), Mean±SD (n=2) ;
YL205 does not bind to NaPi2b negative cells (SK-OV-3, B);
YL205 binds to both high (OVCAR3, C) and low (NCI-H441, D) NaPi2b expressing cells with high affinity.

Internalization in Tumor Cells

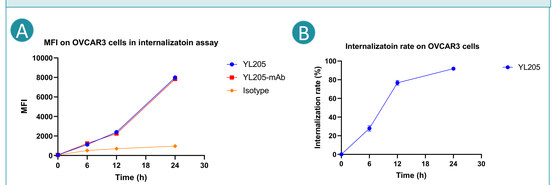
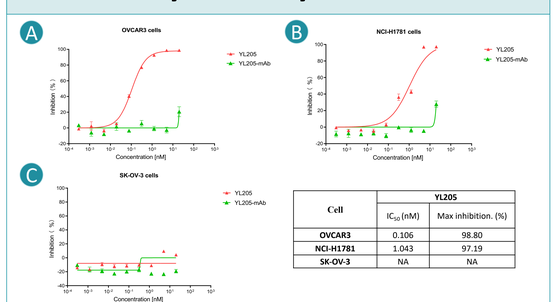


Figure 4. YL205 can be internalized into OVCAR3 cells in high efficiency.

In vitro Cytotoxicity in Tumor Cells



Cell	YL205	
	IC_{50} (nM)	Max inhibition. (%)
OVCAR3	0.106	98.80
NCI-H1781	1.043	97.19
SK-OV-3	NA	NA

Figure 5. YL205 shows potent cytotoxicity in NaPi2b high OVCAR3 cells (A) and NaPi2b medium NCI-H1781 cells (B), but no activity in NaPi2b negative SK-OV-3 cells (C).

YL205 Induces Tumor Cell Apoptosis

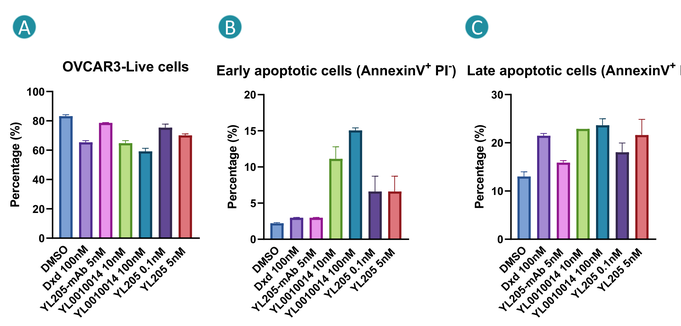


Figure 6. YL205 and its payload YL0010014 kill OVCAR3 tumor cells by inducing apoptosis .

In vivo Anti-tumor Activity of YL205

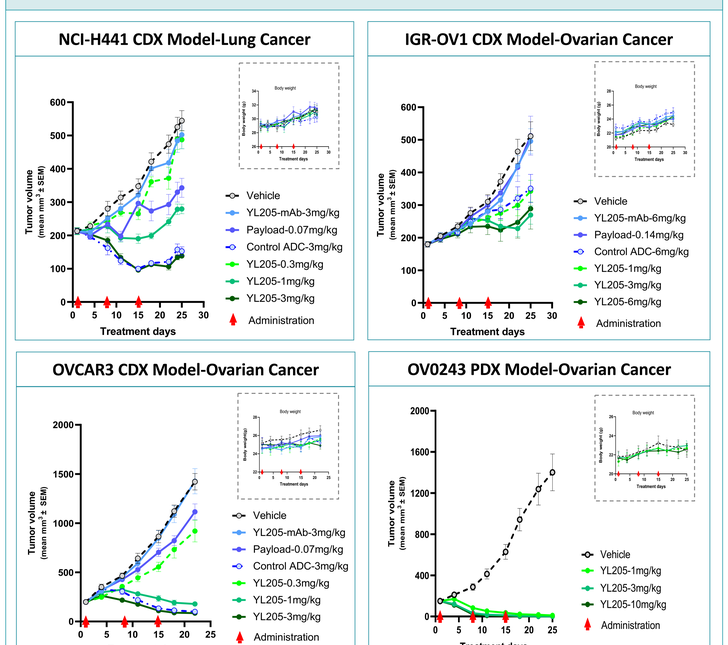


Figure 7. YL205 shows potent anti-tumor activity in xenograft models with different levels of NaPi2b expression (Low: NCI H441; High: OVCAR3, IGR-OV3, and OV0243).

Payload Release of YL205 in Plasma

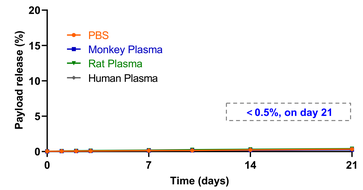


Figure 8. The payload release of YL205 is all less than 0.5% upon 21 days' incubation in plasma of monkey, rat and human. The rate of release of the payload (YL0010014) is calculated using the ratio of the average concentration of YL0010014 released to the total concentration.

PK Profile of YL205 in Cynomolgus Monkey

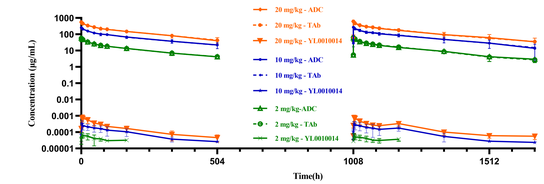


Figure 9. YL205 shows linear PK profile in cynomolgus monkey. Overlapping of ADC and total antibody (TAb) PK curves and low concentrations of free payload (YL0010014) indicates YL205 is highly stable in circulation. Doses up to 20mg/kg are well tolerated by animals.

Conclusions

- YL205 is a next generation ADC targeting NaPi2b with novel linker-payload and homogeneous DAR of 8.
- YL205 binds to human NaPi2b with high affinity and specificity.
- YL205 can be efficiently internalized into tumor cells and induce cell apoptosis.
- YL205 demonstrates potent *in vitro* and *in vivo* anti-tumor activity in tumor cells or xenograft models with different levels of NaPi2b expression.
- YL205 is highly stable in circulation of cynomolgus monkeys and well tolerated by animals.
- These favorable characteristics of YL205 warrants its further clinical development in tumors expressing NaPi2b.

References

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2. Bondeson DP, et al. Nat Cancer. 2022.
3. Banerjee S, et al. Cancer Treat Rev. 2023.

Email: info@medilinkthera.com