MediLink's TMALIN® ADC Linker Technology: Tumor Microenvironment Specific Extracellular and Intracellular Double Cleavage Mechanism for Better Efficacy and Expanded Target Space

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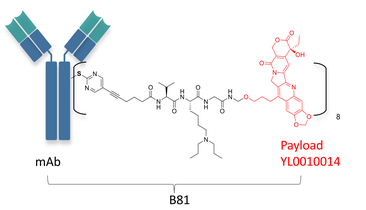
Introduction

- The intracellular lysosomal payload release mechanism utilized by most commercial ADCs is most effective for targets with high tumor antigen expression but may encounter ADC resistance issues due to intracellular trafficking kinetics.
- A novel systemically stable and extracellular tumor microenvironment-activatable linker (TMALIN®) technology has been developed. Studies have been carried out to characterize the drug-to-antibody ratio (DAR), hydrophilicity, and to investigate the mechanism of payload release in tumor microenvironments.
- The anti-tumor efficacy of ADCs has also been assessed in CDX and PDX models. Additionally, both in vitro and in vivo stabilities of the TMALIN® antibody-drug conjugates have been evaluated through a series of preclinical studies..

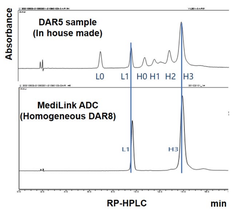
Characterization of TMALIN® ADC

Payload-linker Structure



- **mAb**: recombinant human immunoglobulin G1
- **B81**: cleavable tripeptide linker and payload
- **Payload**: YL0010014, a topoisomerase I inhibitor, exhibits higher cellular potency than DXd.

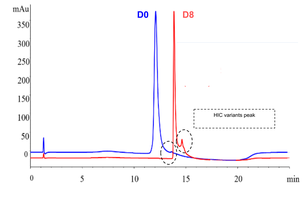
Homogeneous DAR8



L0: Light chain with 0 B81
L1: Light chain with 1 B81
H0: Heavy chain with 0 B81
H1: Heavy chain with 1 B81
H2: Heavy chain with 2 B81
H3: Heavy chain with 3 B81

- RP-HPLC chromatogram of MediLink ADC shows only L1 and H3 detected, indicating **high homogeneity of DAR 8**.

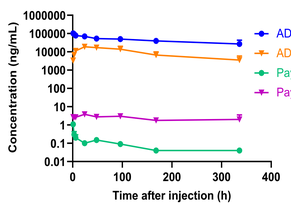
High Hydrophilicity



- The peak of MediLink ADC (D8) is close to that of the mAb (D0) in HIC chromatogram, indicating the **hydrophilicity is not significantly impacted by the conjugation**.

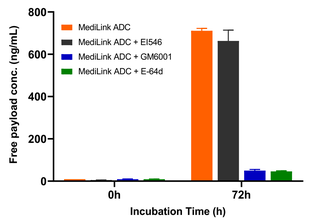
Specific Release of Payload in Tumor Microenvironment

PK in mice receiving ADC of 10 mg/kg



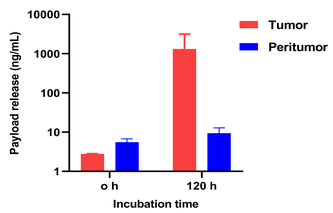
- The concentration of payload in the tumors is significantly higher than that in the serum, while the concentration of ADC in the serum was higher than in the tumor.

ADC incubation with inhibitor in CDX tumor homogenate



- The release of payload could be inhibited by GM6001 (pan-MMP inhibitor) or E-64D (pan-cysteine protease inhibitor), but not by EI546 (elastase inhibitor).

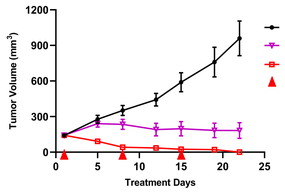
ADC incubation in human breast cancer homogenate



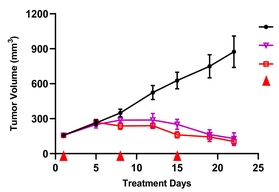
- The payload release is remarkably faster in tumor than in peritumor, indicating the specific release of payload in tumor microenvironment.

High Efficacy of TMALIN® Non-internalizing ADCs

ES0204 PDX Model (ESCC)



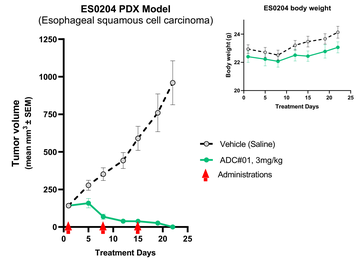
PR9586 PDX Model (Prostate Cancer)



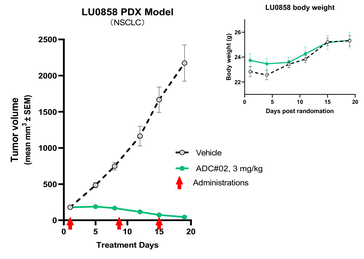
- B81 conjugated to non-internalizable control IgG (IgG-B81 in purple) is highly efficacious in ES0204/PR9586 PDX model, indicating that extracellular payload release is effective for cancer treatment.

Anti-tumor Effect on PDX Models

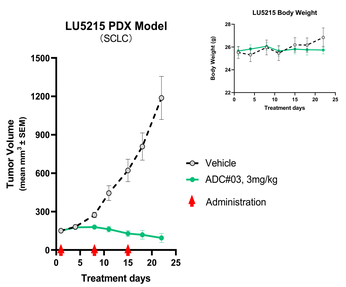
Esophagus cancer PDX model [1]



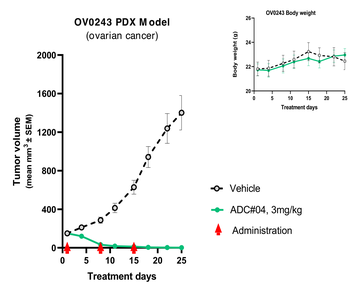
Non-small cell lung cancer PDX model [2]



Small cell lung cancer PDX model [3]



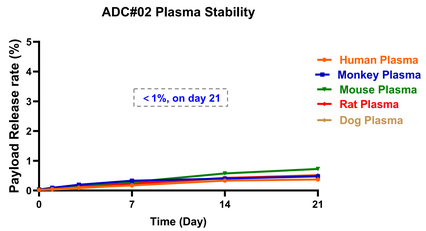
Ovarian cancer PDX model [4]



- MediLink ADCs are well tolerated and have demonstrate outstanding anti-tumor efficacy in various PDX models, such as non-small cell lung cancer, small cell lung cancer, colorectal cancer, ovarian cancer, etc.

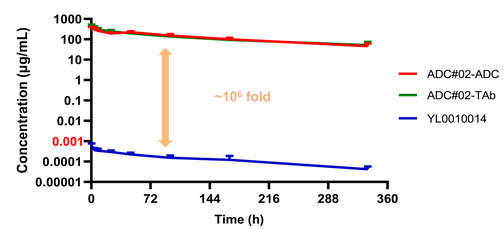
High Stability in The Systematic Circulation

ADC incubation in plasma



- Less than 1% of the payload released after 21-day incubation with human, monkey, dog, rat and mouse plasma under 37 °C.

PK profiles of ADC in monkey



- PK curves of ADC and total antibody (TAb) are almost identical;
- Amount of free toxin is extremely low;
- TMALIN® ADC is stable in cynomolgus monkeys.

Conclusions

- TMALIN® ADC platform uses an irreversible pyrimidine coupling technology to prevent classical maleimide based linker-payload exchange reactions with Albumin.
- TMALIN® ADCs are highly hydrophilic and can be coupled with various antibodies without causing ADC aggregation.
- TMALIN® linker can be cleaved both intracellularly as normal and extracellularly in tumor microenvironments.
- TMALIN® ADCs exhibit favorable *in vivo* efficacy in various animal models regardless internalization or not.
- TMALIN® ADCs show high stability both *in vivo* and *in vitro*.
- TMALIN® ADCs are well tolerated in monkeys, showing no abnormalities in clinical signs or pathology.

References

1. AACR 2023, Abstract#6304.
2. AACR 2023, Abstract#563.
3. ELCC 2024, FRN#241P.
4. AACR 2024, Abstract#1894.

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