Zymeworks Topoisomerase 1 Inhibitor ADC Platform: From Concept to Pipeline

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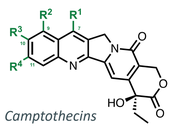
Background: Camptothecin Therapeutics



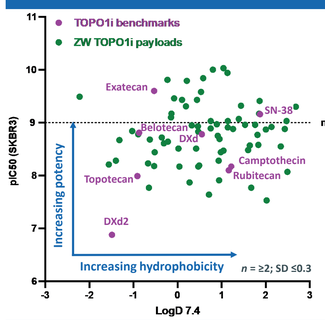
Camptothecins

Potent inhibitors of topoisomerase I:

- Discovered in the early 1960 by M. E. Wall and M. C. Wani of Research Triangle Institute[1]
- Isolated from *Camptotheca acuminata* (The Happy Tree)
- Prevents DNA re-ligation which results in double strand breaks and apoptosis

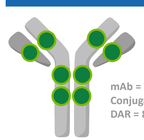
- **3 approved small molecules** (Topotecan, Irinotecan, Belotecan)[2]
- **2 approved ADCs** (Enhertu®, Trodelvy®)
- **Several ADCs**, **SMDCs**, and **NPs** at different stages of development

Zymeworks Camptothecin Payloads Span a Range of Potency and Hydrophilicity

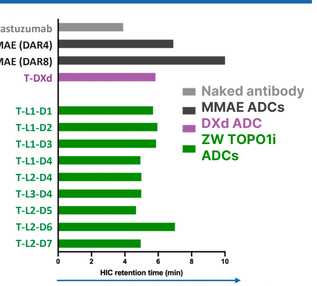


- ✓ ~100 new TOPO1i payloads (R^2 = H, prepared in 1-6 steps)
- ✓ Range of potency and hydrophilicity
- ✓ Two linking strategies (from R^1 and R^3 groups)

Zymeworks TOPO1i Drug-linkers Yield ADCs with Favorable Physiochemical Properties and Low Aggregation



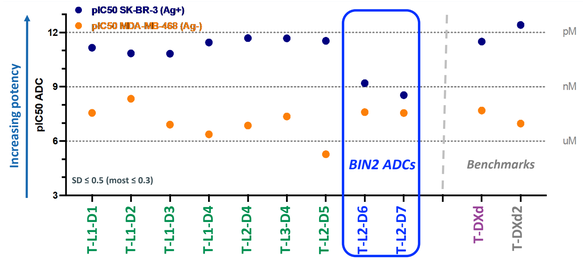
mAb = Trastuzumab
Conjugation = cysteine
DAR = 8



ADCs with ZW TOPO1i DLs:

- ✓ No aggregation for DAR8 (*challenge for this class*)
- ✓ Hydrophilic
- ✓ 100% monomeric
- ✓ Robust freeze thaw stability

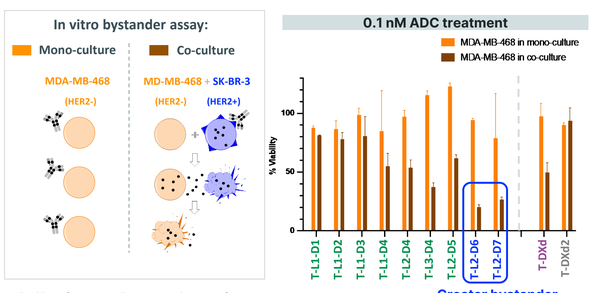
Lead ADCs Showed Good Potency and Selectivity in 2D Cytotoxicity Assays



Representative pIC50 in an Ag+ cell line sensitive to TOPO1i ADCs and an Ag- cell line
>70 cell lines tested in 2D assays with 8 different TAA TOPO1i ADCs (~25% sensitive)

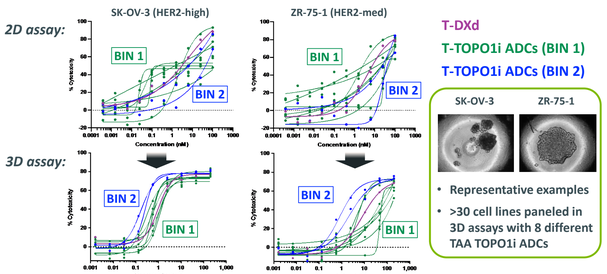
Bin 2 ADCs Demonstrate Greater Bystander Activity and Superior Potency in Spheroid Assay

Greater bystander activity for bin 2 ADCs



Viability of **Ag-** cell line determined by flow cytometry
Viability of **Ag+** simultaneously measured (~80-100% cytotox; not shown)

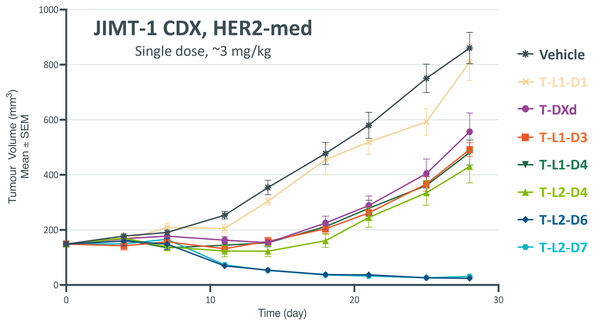
Spheroid assay altered the potency ranking of ADCs

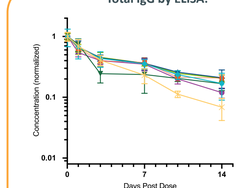


T-DXd
T-TOPO1i ADCs (BIN 1)
T-TOPO1i ADCs (BIN 2)

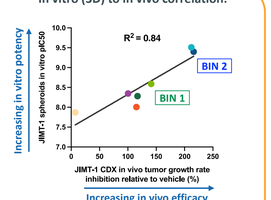
- Representative examples
- >30 cell lines paneled in 3D assays with 8 different TAA TOPO1i ADCs

Zymeworks TOPO1i ADCs Demonstrate Potent in vivo Efficacy



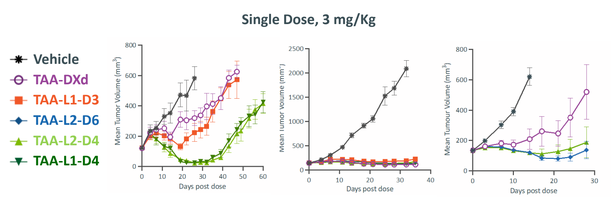


All test articles (except T-L1-D1) showed comparable PK profile, within assay variability



3D *in vitro* cytotoxicity better correlates with *in vivo* efficacy

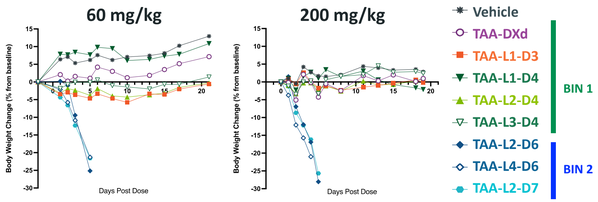
Zymeworks TOPO1i ADCs Demonstrate Anti-tumor Activity in Multiple *in vivo* Models



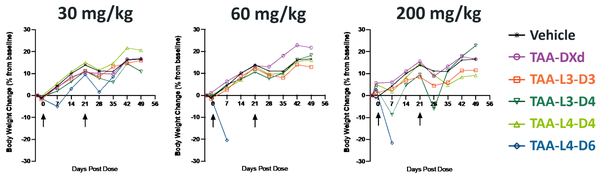
TAA	TAA1	TAA2	TAA3
Model	Ovarian CDX	Lung CDX	Solid tumor CDX
Target Expression Level	Med/Low, Heterogeneous	High	High/Med, Heterogeneous
Mice per group	6	6	6

Murine and Rat Tolerability Studies Identified 2 Lead Drug Linkers

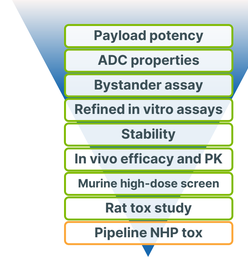
4 drug-linkers were tolerated in murine high dose screen



2 lead drug-linkers were identified in rat tox study



The Path from Concept to Pipeline



- Identify leads from ~100 TOPO1i payloads
- Comparable efficacy to industry leading DXd platform across different targets
- Two lead drug-linkers identified after rat tox study
- Pipeline NHP tox studies initiated
- Multiple pipeline programs in development

References

1. Monroe E. Wall, M. C. Wani, C. E. Cook, Keith H. Palmer, A. T. McPhail, and G. A. Sim, *Journal of the American Chemical Society* **1966** *88* (16), 3888-3890
2. Irinotecan and Topotecan are FDA approved. Belotecan is approved in South Korea

Acknowledgements

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