N-Myristoyltransferase (NMT) inhibitors as differentiated payloads for Antibody Drug Conjugates

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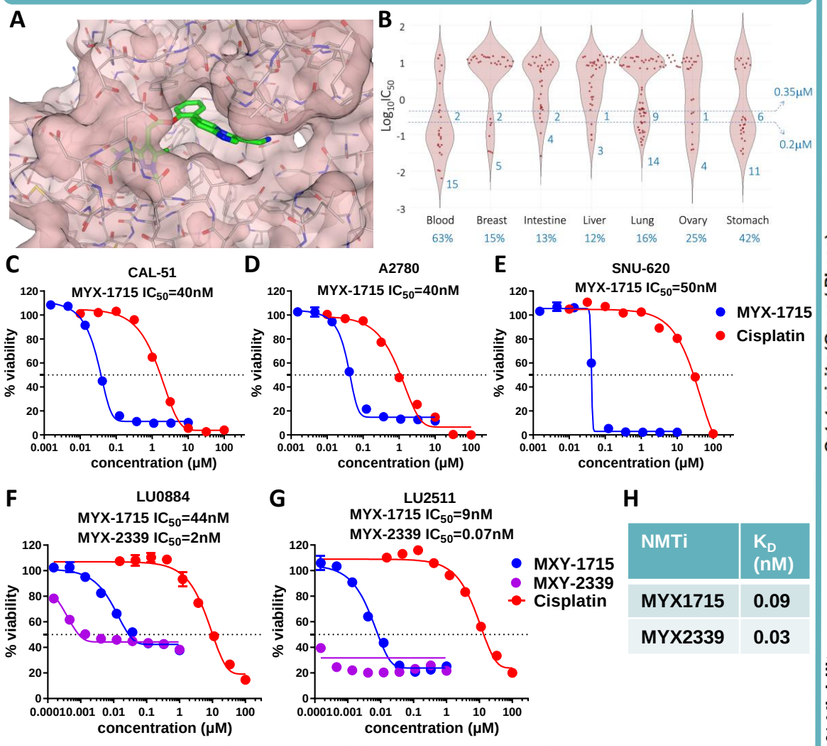
Introduction

N-myristoylation is the N-terminal modification of proteins with myristic acid, a 14-carbon fatty acid. Catalysed by two enzymes, N-myristoyltransferase (NMT1, NMT2), this modification can be co- or post-translational [1]. NMT inhibitors (NMTi) have been shown to inhibit viability and growth of haematological cancers [2]. Here, we have developed novel highly potent and selective NMTi which are cytotoxic in multiple cell lines as well as exhibit tumour regression in *in vivo* models. To explore targeted delivery of NMTi, we tethered a selective NMTi to trastuzumab (HER2+ mAb) to produce an antibody drug conjugate (ADC) – MYX2449 which was profiled *in vitro* and *in vivo.*

Cytotoxic effects of NMTi in cancer cell lines



H

NMTi	K_D (nM)
MYX1715	0.09
MYX2339	0.03

Figure 1: Structure of MYX1715(A). Absolute IC_{50} of MYX1715 in 250 cancer cell lines across 7 tissues (B). IC_{50} of MYX1715 in breast (CAL51), ovarian (A2780) and gastric (SNU620) cancer cell lines (C-E). IC_{50} of MYX1715 and MYX2339 in NSCLC PDXs (F-G). Dissociation constant (K_D) of NMTi (H)

NMTi is efficacious in *in vivo* B-cell lymphoma and ovarian cancer models

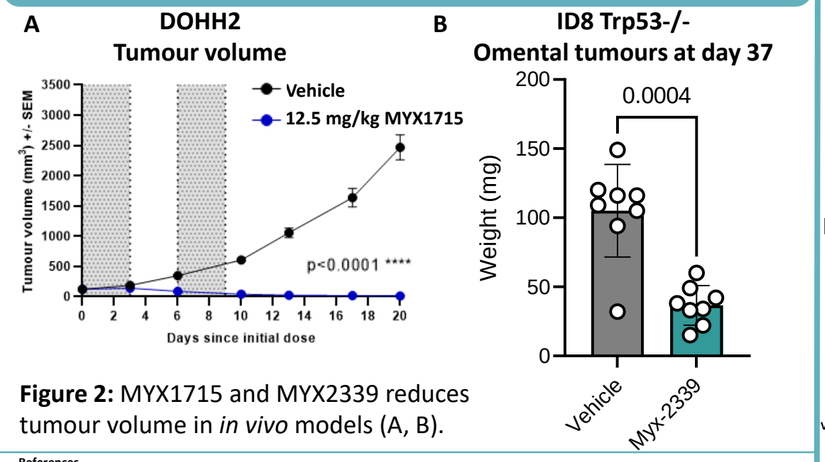
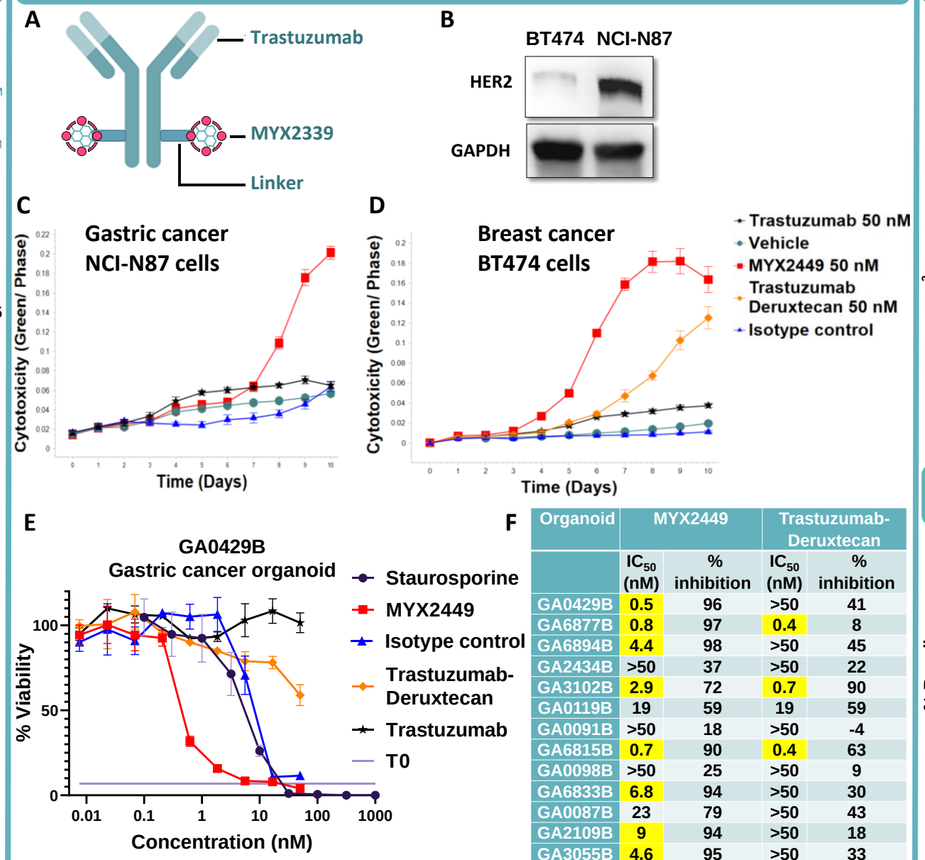


Figure 2: MYX1715 and MYX2339 reduces tumour volume in *in vivo* models (A, B).

References
1. Wright MH, Heal WP, Mann DJ, Tate EW. Protein myristoylation in health and disease. J Chem Biol 2010 Mar;3(1):19-35.
2. Beauchamp E., Yap M.C., Iyer A. et al. Targeting N-myristoylation for therapy of B-cell lymphomas. Nat Commun 2020; 11(1): 5348

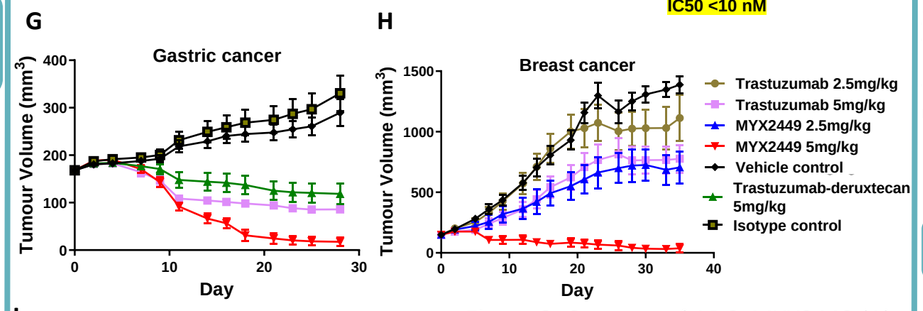
Antitumour efficacy of NMTi - ADC, MYX2449



F

Organoid	MYX2449		Trastuzumab-Deruxtecan	
	IC_{50} (nM)	% inhibition	IC_{50} (nM)	% inhibition
GA0429B	0.5	96	>50	41
GA6877B	0.8	97	0.4	8
GA6894B	4.4	98	>50	45
GA2434B	>50	37	>50	22
GA3102B	2.9	72	0.7	90
GA0119B	19	59	19	59
GA0091B	>50	18	>50	-4
GA6815B	0.7	90	0.4	63
GA0098B	>50	25	>50	9
GA6833B	6.8	94	>50	30
GA0087B	23	79	>50	43
GA2109B	9	94	>50	18
GA3055B	4.6	95	>50	33
GA6866B	0.4	98	0.4	85
GA0060B	3.7	99	>50	37

IC50 <10 nM



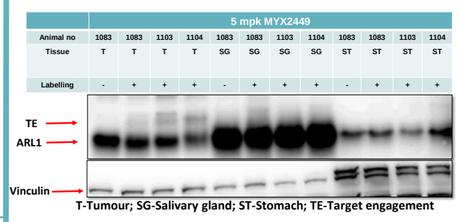


Figure 3: Cartoon of ADC, MYX2449 (A). Expression of HER2 in breast (BT474) and gastric (NCI-N87) cancer cell lines (B). Antitumour effects of MYX2449 in cell lines (C,D) and in gastric cancer (GC) PDX organoids (E,F). Antitumour effects of MYX2449 in GC (G) and breast cancer (H) xenograft models. Target engagement in GC xenograft (I).

MYX2449 exhibits good bystander effect in cell lines

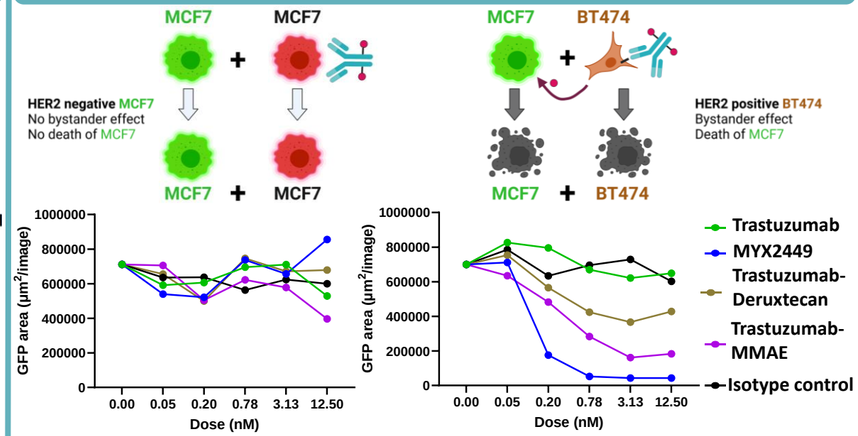


Figure 4: Bystander effect of MYX2449.

In vivo tolerability of MYX2449

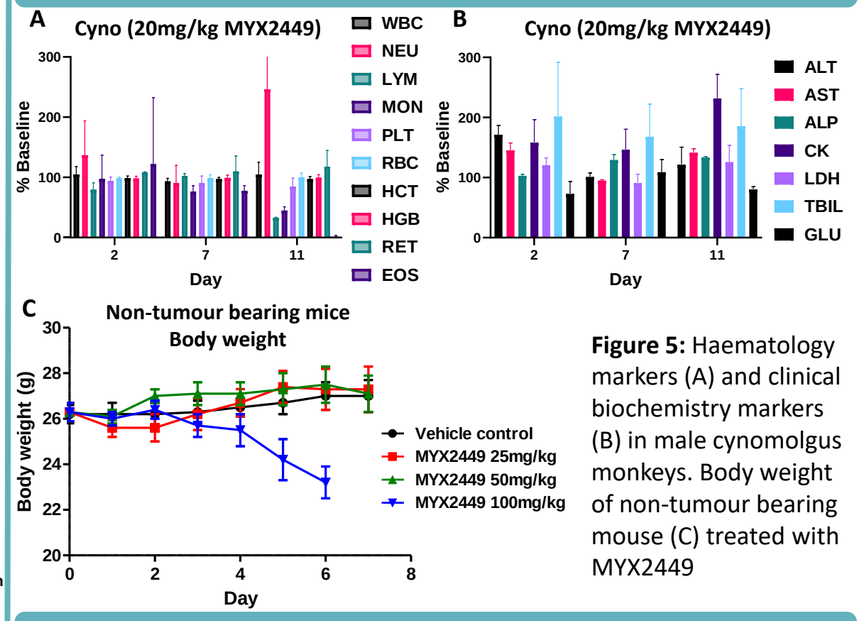


Figure 5: Haematology markers (A) and clinical biochemistry markers (B) in male cynomolgus monkeys. Body weight of non-tumour bearing mouse (C) treated with MYX2449

Conclusion

NMTi are efficacious *in vitro* and i*n vivo* and can readily be conjugated to therapeutic mAbs to generate ADCs. The ADC, MYX2449 demonstrated cytotoxic potency in cell lines, antitumour efficacy and specificity in both high and low HER2 expressing cancers with tolerability up to 10 times its efficacious dose in *in vivo* models. In preclinical models of GC, MYX2449 delivered differentiated activity compared to trastuzumab-deruxtecan. NMTi represent a novel class of ADC payloads that can be exploited as targeted therapies in cancer.

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