Glymab® ADC's for targeting cancers with high unmet need

Fucosyl-GM1 and Lewis^{y} : internalising targets for SCLC and multiple solid tumours

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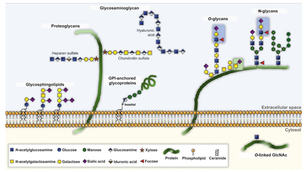
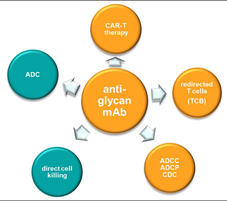


BACKGROUND

- Glycosylation regulates a range of cellular functions
- Altered glycosylation is a cancer hallmark => ideal target for **antibody development**
- The same glyco-epitopes can be present on a range of glycoproteins (GP) and/or glycolipids

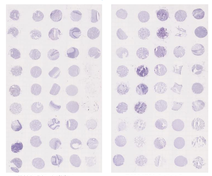
Multiple approaches to targeting cancer cells: direct cell killing, effector functions, redirecting T cells, CAR-T and **drug delivery (ADC)**

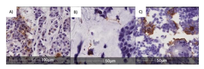


SC134 - specifically binding fucosyl-GM1, for effective SCLC targeting with ADC

- Fucosy-GM1 (FucGM1) is selectively expressed in over 80% of patient-derived (PDX) SCLC tumour tissues, but is virtually absent from normal healthy tissue
- H134 targets FucGM1 with high avidity and specificity
- H134 – ADC exhibits potent anti-tumour impact across a range of MOA (topoI, anthracylin (PNU) and DNA-monoalkylator) and DAR

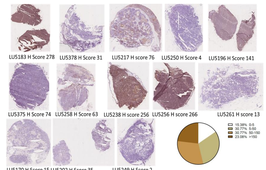
Absence of FucGM1 in normal healthy tissues

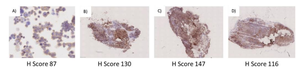




Pituitary (1/3), skin (2/3) and thymus (3/3) are the only three FucGM1 positive healthy tissues

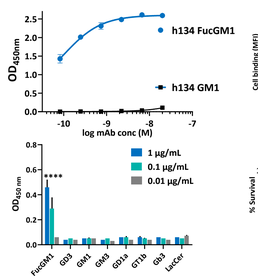
Widespread FucGM1 SCLC tumour distribution (PDX)





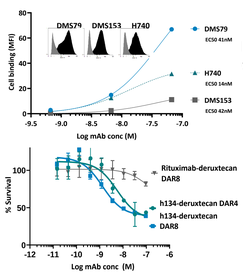
h134 binds to over 80% of SCLC PDX tissues
DMS79 is a valid SCLC tumour model
([a]lab-grown, [b-d]tumour xenograft)

H134 only binds FucGM1



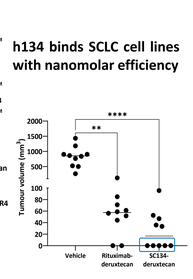
h134 binds with nanomolar avidity to FucGM1, no cross-reactivity with GM1 nor other glycolipids

H134-Deruxtecan (DAR4 and DAR8) - potent DMS79 killing



h134 binds SCLC cell lines with nanomolar efficiency

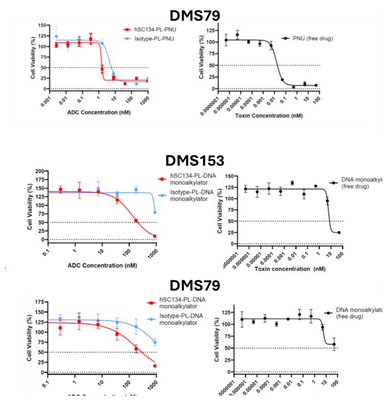
Nanomolar *in vitro* DMS79 killing by h134-Deruxtecan ADC (produced by Sterling Pharma)



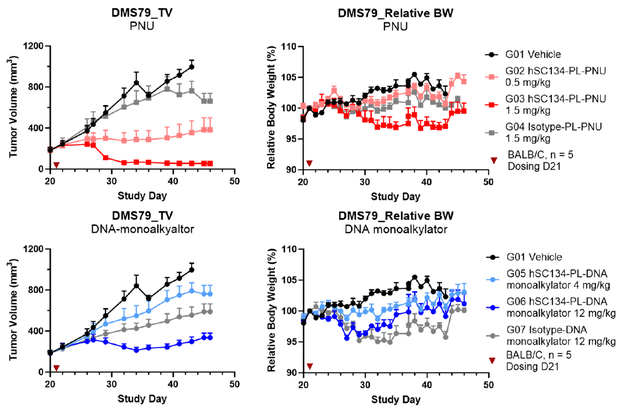
Enhanced *in vivo* tumour-free survival (DMS79 CDX model)

Potent dose and target-dependent tumour killing by h134 ADC (PNU and DNA mono-alkylator)*

*Results courtesy of Iksuda Therapeutics



Dose-dependent *in vitro* cytotoxicity by h134-PNU (DAR2) and DNA monoalkylator (DAR2-3) on DMS79 and DMS153



In vivo DMS79 tumour eradication by h134-PNU (anthracycline) and h134-monoalkylator

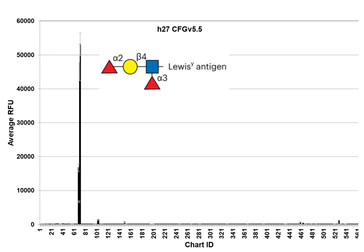
H134 (FucGM1) ADC ideal candidate therapeutic for SCLC treatment

- ✓ FucGM1: binds fucosyl GM1 specifically and with nanomolar avidity making it an extremely selective ADC therapeutic for SCLC, which currently has a high unmet need
- ✓ H134-ADC: potent anti-tumour impact *in vitro* and *in vivo*

SC27 - monospecific targeting of Lewis^{y} on a broad range of tumours

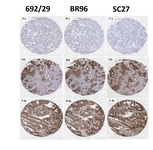
- Monospecificity for Lewis^{y} results in less binding to normal tissues compared to other Lewis$^{y, b, x}$ cross-reactive mAbs
- SC27 targets over >50% of gastric and colorectal cancers and >30% ovarian and breast cancers
- Effective drug delivery by SC27-ADC; primary gastric epithelial cells can be spared by tailoring the ADC drug

SC27 is monospecific for Lewis^{y}



Lewis^{y} is the ONLY SC27 binding glycan out of >600 glycans on a high-density glycan array

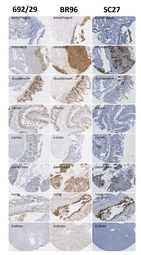
SC27 binds multiple solid tumour types



Tumour type	% Positive
Gastric	69
Colorectal	55
Ovarian	36
Breast	39

SC27 binds a wide range of tumour types, but exhibits a more restricted normal tissue distribution, compared to Lewis$^{y/b/x}$ cross-reactive comparators (BR96, 692/29)

More restricted SC27 binding to normal tissue

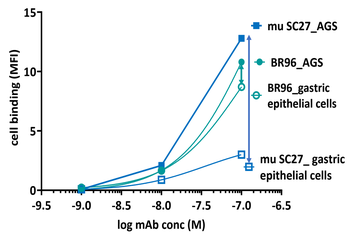


SC27 is an effective drug delivery (ADC) mAb

drug delivery (Moradec anti-hu Fab-conjugated drugs)			
SC27	MMAE (EC50, nM)	PNU (EC50, nM)	DX8951 (EC50, nM)
AGS^{hi}	0.5	0.1	0.08
MCF7^{mod}	N/A	0.3	0.3

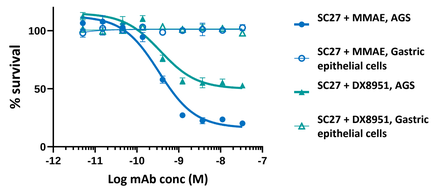
SC27 exhibits subnanomolar drug delivery efficiency across high and moderate Lewis^{y} -expressing cancer cell lines

Murine SC27 is more selective in gastric tumour cell binding compared to BR96



Murine SC27 shows wider differential binding between gastric adenocarcinoma cell line and primary gastric epithelial cells compared to BR96

Off-tumour targeting can be avoided using mono-Lewis^{y} specific SC27



Safe targeting of gastric adenocarcinoma (AGS), avoiding normal gastric epithelium toxicity (primary cells), using SC27 in combination with auristatin (MMAE) or topoisomerase inhibitor (DX8951)

SC27-ADC for Lewis^{y} positive tumour treatment

- ✓ SC27 mono-specificity widens the therapeutic window, avoiding off-tumour toxicity against normal gastric epithelium seen with BR96-ADC
- ✓ SC27-ADC: potent tumour cell killing in vitro across a range of drugs