GlyMabs, glycome-targeting monoclonal antibodies for cancer therapy

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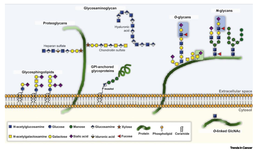
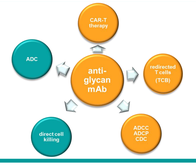
INTRODUCTION



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

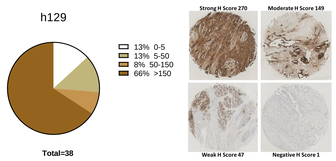
Multiple approaches to targeting cancer cells: direct cell killing, effector functions, redirecting T cells, CAR-T and drug delivery (ADC)



SC129 - recognising sialyl-di-Lewis^a with high specificity, delivers warheads with subnanomolar potency

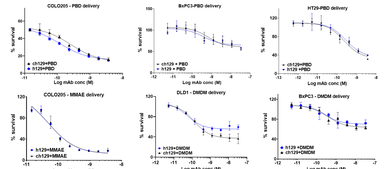
- humanised 129 (h129) targets highly expressed Sialyl-di-lewis^a glycan in pancreatic tumour tissue with limited normal tissue expression.
- h129 binds its glyco-target with nanomolar affinity
- h129 exhibits efficient drug delivery, across a range of MOA and cancer cell lines
- SC129-ADC has *in vivo* anti-tumour activity

Tumour distribution



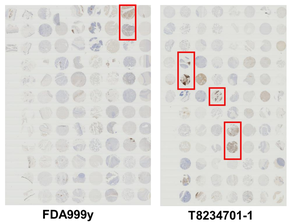
h129 binds to 87% (33/38) of pancreatic cancers, 66% (25/38) with strong, 8% (3/38) moderate and 13% (5/38) with weak intensity.

129 ADC conjugates

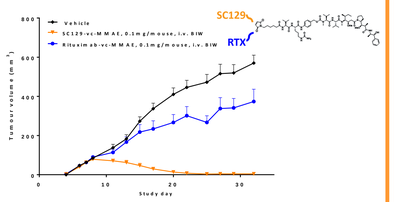


Various drug delivery into high target expressing cancers cells by h129 in comparison to ch129.

Normal tissue distribution



h129 exhibits restricted normal tissue distribution with moderate binding to pancreas, thyroid and prostate, rendering it an attractive candidate for ADC, CAR-T or T cell bispecific development



SC129 conjugated to the tubulin inhibitor MMAE (auristatin) via a val-cit cleavable linker shows significant anti-tumour activity *in vivo* (COLO205); the isotype control (Rituximab, RTX), shows limited impact

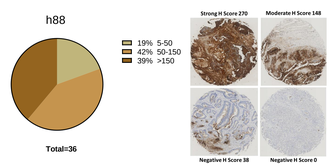
Reference

Mol Cancer Ther. 2020 Mar;19(3):790-801

SC88 - targeting Lewis$^{a/c/x}$ on extended tumour types has direct inflammatory cell killing (ICD) ability

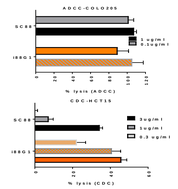
- h88 binds to unique glycan (Lewis$^{a/c/x}$) on GP and GL
- h88 targets 100% of colorectal tumours on TMAs with restricted normal tissue distribution
- AvidiMab^{TM} technology introduces intermolecular cooperativity => enhanced target avidity
- AvidiMab^{TM}-engineered SC88, i88G1, exhibits inflammatory cell killing (ICD) through pore formation

Tumour distribution



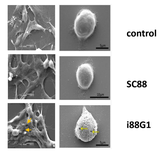
h88 binds to 100% (36/36) of colorectal cancers, 39% (14/36) with strong, 42% (15/36) moderate and 19% (7/36) with weak intensity.

Effector functions



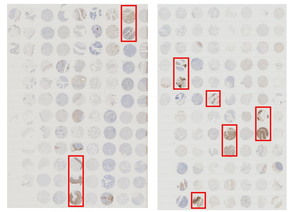
Comparable ADCC and CDC activity by AvidiMab^{TM} i88G1 and SC88

Direct cell killing (ICD)



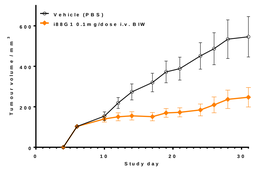
Pore formation (arrows) through high-level avid binding by AvidiMab^{TM} i88G1 (HCT15, left; COLO205, right)

Normal tissue distribution



h88 exhibits restricted normal tissue distribution with moderate binding to pancreas, colon, thyroid and prostate, rendering it an attractive candidate for ADC, CAR-T or T cell bispecific development

COLO205 *in vivo* CDX



Effective anti-CDX activity by AvidiMab^{TM} i88G1 in nude mice

References

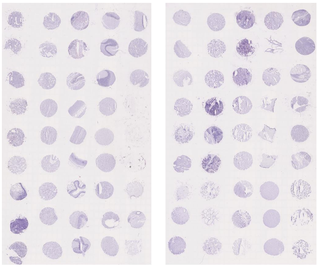
Clin Cancer Res. 2015 Jul 1;21(13):2963-74

Cancer Res. 2020 Aug 15;80(16):3399-3412

SC134 - specifically binding fucosylGM1, for effective SCLC targeting

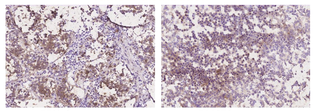
- h134 binds to patient derived xenograft (SCLC PDX) with high specificity with no normal tissue binding.
- h134 exhibits efficient drug delivery across DMS79 cancer lines

Normal tissue distribution

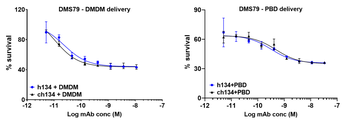


h134 shows no binding to healthy array making it an attractive candidate for cancer therapy.

Tumour distribution



h134 binds to patient derived xenografts and DMS79 tumours

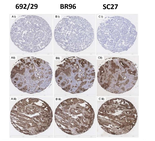


Fab-DMDM (left) and IgG-PBD (right) drug delivery into high target expressing DMS79 cells by h134 in comparison to ch134

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

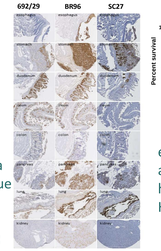
- Monospecificity for Lewis^y results in less binding to normal tissues compared to other Lewis^y mAbs
- SC27 targets over 55% of colorectal, 86% gastric, 38% ovarian and 46% breast cancer tissues
- SC27 exhibits *in vivo* anti-tumour activity
- AvidiMab^{TM} engineered SC27, i27G1 exhibits improved functional affinity and direct cell killing

Tumour distribution

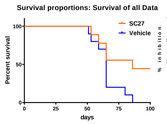


SC27 binds a wide range of tumour types, but exhibits a more restricted normal tissue distribution, compared to Lewis$^{y/b/x}$ cross-reactive comparators (Br96, 692/29)

Normal tissue distribution

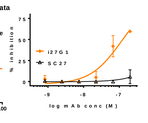


HCT15 *in vivo* CDX



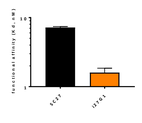
effective anti-CDX activity by SC27 in the high-metastasising HCT15 model

Direct cell killing



AvidiMab^{TM} i27G1 displays pronounced proliferation inhibition on Lewis^y + AGS cells

SPR target binding analysis



AvidiMab^{TM} i27G1 shows enhanced functional Lewis^y affinity (reduced Kd)

CONCLUSIONS

- **Altered glyco-forms expressed by cancer cells afford great targets for therapeutic antibody development**
- **Expression of the same glycan on a variety of proteins and lipids → multiple approaches to targeting cancer cells**
- **Glymab antibodies multimodal development potential for targeted cancer therapy**