Treatment of solid tumors with antibody drug conjugates targeting aberrant O-glycoproteins

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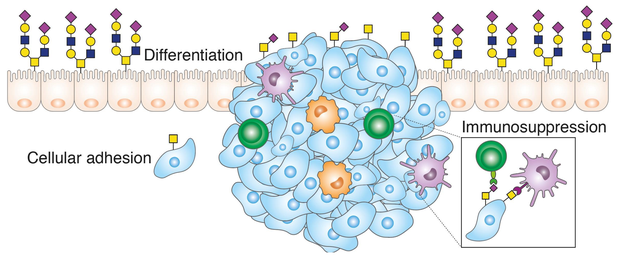
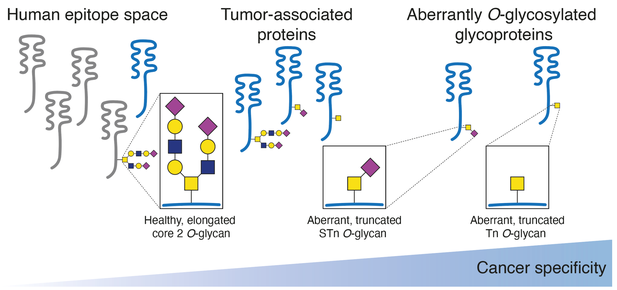
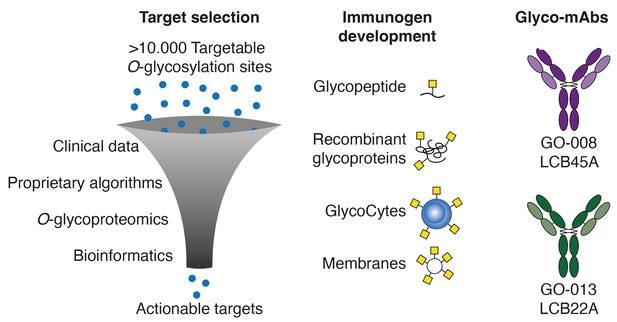
O-glycans affect cancer hallmarks



Cancer specific aberrant *O*-glycans

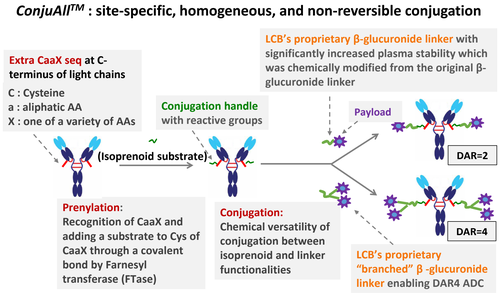


Strategy



ADC platform - *ConjuAll*™

***ConjuAll*™ : site-specific, homogeneous, and non-reversible conjugation**



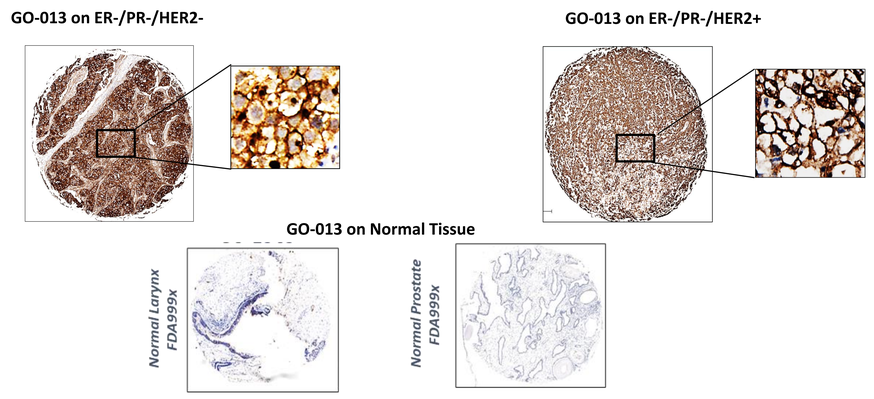
In vitro cytotoxicity

ADC	*In vitro* cytotoxicity in cancer cells (EC50)				
	MCF7M	T3M4M	OVCAR3M	T47DM	PANC1M
LCB22A	63 nM	N/A	N/A	4.3 nM	N/A

ADC	*In vitro* cytotoxicity in normal cells (EC50)		
	Fa2N4 (Liver)	HK2 (Kidney)	hPBMC (blood)
LCB22A	>1000 nM	501 nM	574 nM

***In vitro* cytotoxicity of LCB22A (GO-013).** LCB22A shows potent activity against breast cancer cell lines. LCB22A shows low toxicity to normal cell lines.

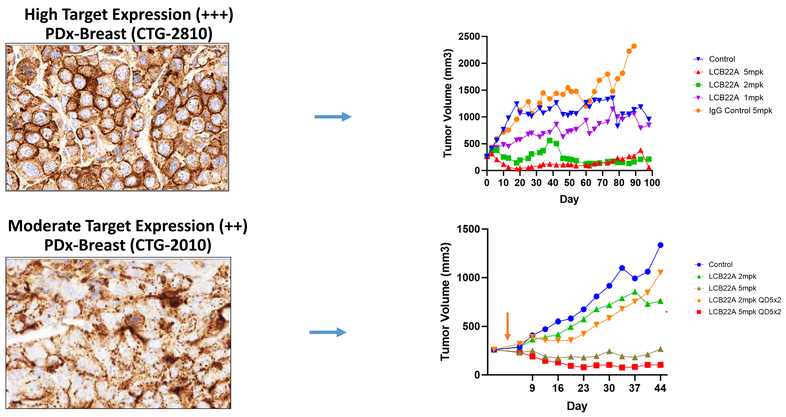
GO-013 selectively react with cancer tissues



Tissues	Positive Surface Stain
Breast Cancer (non-metastatic; IDC, including TNB)	**28%** (24/85)
Lung	**13%** (15/120)
Normal	**0%** (0/96)

GO-013 IHC of cancer and normal tissue. "Positive" tissue includes moderate (++) and high (+++) target expression. GO-013 selectively stains the surface of cancer cells.

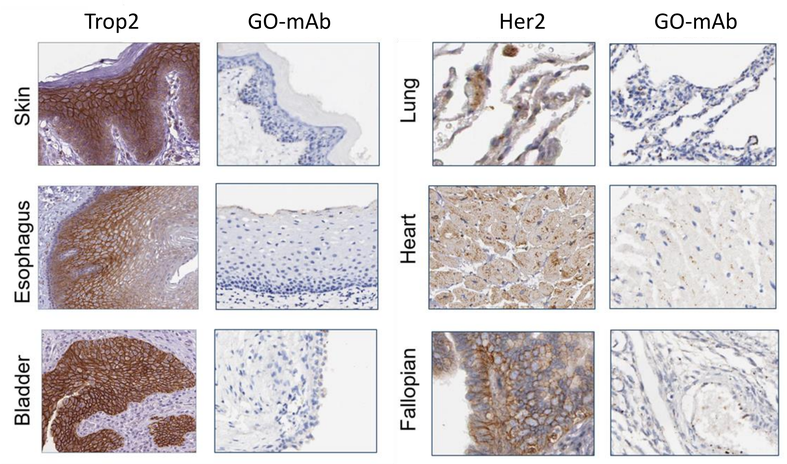
Potent efficacy of LCB22A in PDX models



Model	Target Expression	Receptors (per cell)	TGI	Complete Response
PDx Breast (CTG-2810)	High (+++)	270K	98%	5/6 mice
PDx Breast (CTG-2010)	Moderate (++)	90K	93%	3/6 mice

Potent ADC efficacy in multiple tumor models with moderate and high target expression. The properties of PDx models used for xenograft studies were analyzed. GO-013 expression (receptor counts) was assessed by IHC that was calibrated by flow cytometry (FACS) in cultured cells; representative images are shown at 40X magnification. The efficacy of LCB22A was tested in Breast PDx xenograft models. All mice were given either a single dose (day 0) or double dose (arrow head) of ADC (DAR 4).

GO Mabs redefine on/off target toxicities



Abstract

The absence of cancer-selective antibodies impedes solid tumor immunotherapy and targeting aberrantly glycosylated glycopeptide epitopes presents a solution. Our method designs cancer-specific antibodies for novel O-glycoprotein epitopes. Antibody GO-013 specifically targets cancer-specific proteins, validated via Immunohistochemistry and ConjuAll™ technology enables MMAE conjugation (LCB22A), showing potent activity against breast cancers. Cynomolgus monkey toxicity studies demonstrate excellent tolerability, promising effective anti-cancer therapy.

Conclusions

- GO-013 are Tn-glycopeptide specific antibodies with sub-nM binding affinities and exquisite cancer specificities.
- GO-013 is selective for ~28% of all breast cancer types, including triple-negative and metastatic cancers.
- ADC was produced using LigaChem Biosciences' *ConjuAll*™ technology, conjugating the microtubule disrupting payload MMAE via a site-specific beta-glucuronidase cleavable linker (GO-013; LCB22A), with potent activity in vivo (MED ~2mg/kg).
- LCB22A have potent activity in vivo (MED ~2mg/kg).
- GO-013 (LCB22A) is well tolerated at 7.5 mpk in cynomolgus toxicity studies.

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