Preclinical evaluation of HBM7022, an HBICE™ 2+1 CLDN18.2 x CD3 bispecific antibody, for gastric cancer

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Introduction

- Claudin-18.2 (CLDN18.2) is a tetraspan membrane protein involved in the formation of tight junctions. CLDN18.2 is highly expressed in several cancers, including gastric, esophageal, pancreatic, lung, and ovarian cancers.
- CLDN18.2-targeted therapies have shown promising antitumor effects in clinical studies.
- Bispecific T cell engager has the potential to improve the therapeutic window and overcome resistance to targeted therapy. Here we report the development of HBM7022, a CLDN18.2 x CD3 bispecific antibody with our HCAb Based Immune Cell Engager (HBICE™) 2+1 platform. HBM7022 induces potent and specific killing of gastric cancer cells in both *in vitro* and *in vivo* studies.

Results

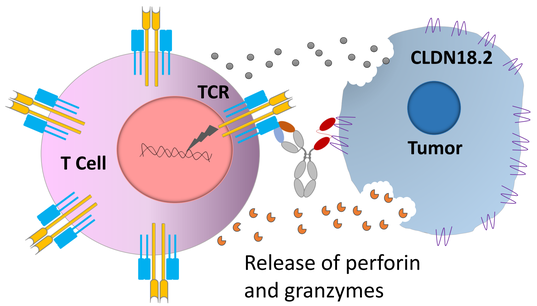
HBM7022: A 2+1 CLDN18.2 x CD3 Bispecific Antibody

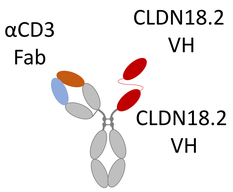
HBICE™ heterodimeric bispecific antibodies can be easily manufactured and purified by standard methods such as protein A and ion exchange chromatography

Anti-CD3:
- Optimized anti-CD3 for less cytokine release
- Monkey cross-reactivity

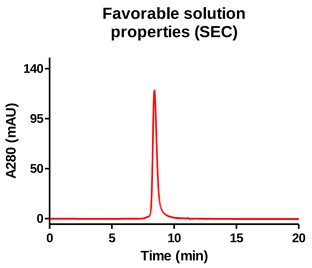
Fc:
- Eliminated FcγR reactivity
- Half-life extension

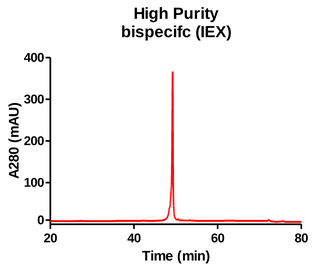
Tandem anti-CLDN18.2 VH:
- High avidity binding
- Fully human heavy chain only antibody





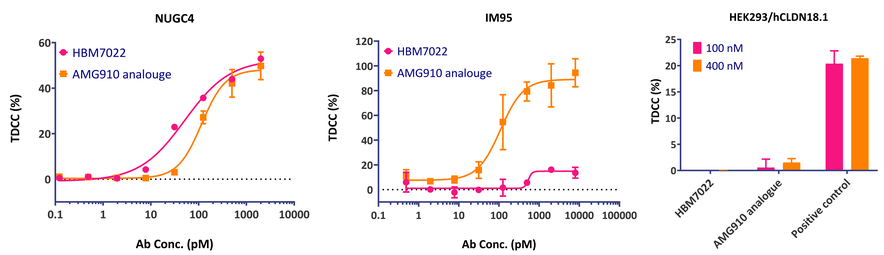
2+1 CLDN18.2 x CD3





Results (continued)

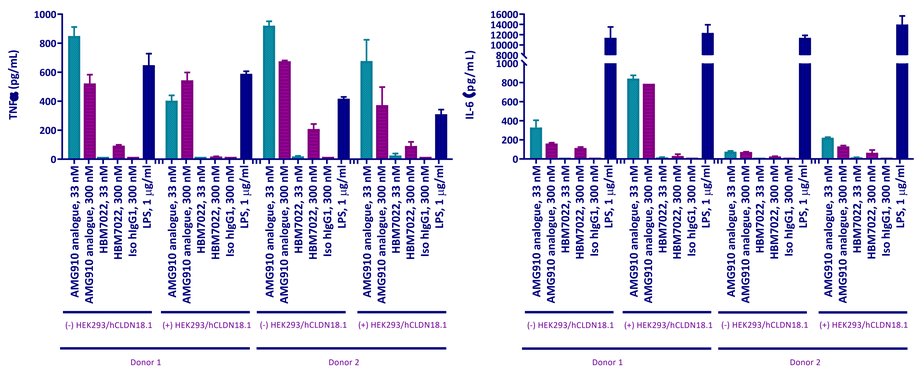
HBM7022 selectively kills tumor cell lines with high CLDN18.2 expression *in vitro*



Activity of HBM7022 was assessed with T cell-dependent cellular cytotoxicity (TDCC) assays. Cell lines were mixed with human pan-T cells at E:T of 5:1, then treated with antibodies for 48 hrs. ND, Not determined.

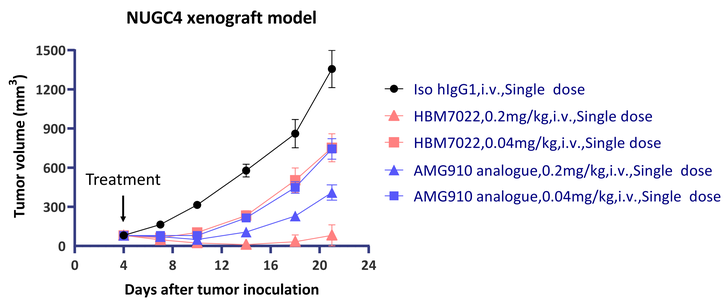
	TDCC EC_{50} (pM)			
Cell line	GSU	NUGC4	SNU-620	IM95
CLDN18.2 expression	High	High	High	Low
HBM7022	53.2	51.3	113	ND

HBM7022 with tuned CD3 activity induces minimal cytokine release *in vitro*



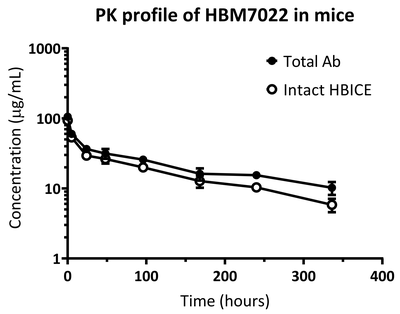
The *In vitro* cytokine release assay; Human PBMCs were incubated with antibodies in the presence or absence of HEK293/hCLDN18.1 cell for 24 hrs. The concentrations of IL-6 and TNFα in the culture medium were quantified by ELISA.

HBM7022 decreases established gastric tumor size



Antitumor activity of HBM7022 against established NUGC4 gastric xenograft tumors; NUGC4 gastric cancer cells and human PBMC were co-injected subcutaneously into NCG mice and allowed to grow to 100-150 mm^3. Treatment was administered by intravenous bolus injection on days 4.

HBM7022 has a favorable pharmacokinetic profile



	5 mg/kg	
Method	Total	Intact
AUC_{last} (μg/mL*hr)	7,395±606	5,714±464
AUC (%)	100	77.2
C_0 (μg/mL)	106	94.1
V_d (mL/kg)	121	132
Cl (mL/hr/kg)	0.50	0.73
$T_{1/2}$ (hr)	173	135

*AUC (%) = AUC / $AUC_{(Total\ assay;\ mean\ value)}$ * 100

Conclusions

HBM7022 is a HBICE™ 2+1 CLDN18.2 x CD3 bispecific antibody:
- The bispecific antibody is easily manufactured and purified.
- It triggers little to none cytokine release in *in vitro* cytokine release assays.
- It Induces potent and specific killing of gastric cancer cells in both *in vitro* and *in vivo* studies.

These results support clinical testing of HBM7022 as a potential therapeutic option for patients with CLDN18.2+ gastric cancer.

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