BCMA x CD3 Bispecific Antibody – A novel HBICE™-based Molecule with Efficient Tumor Killing and Minimal Cytokine Release

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Abstract

B-cell maturation antigen (BCMA), a surface marker highly expressed on malignant plasma cells of multiple myeloma (MM) patients, has been recognized as an ideal target for T-cell redirecting therapies. Currently, T-cell-recruiting bispecific antibodies have shown potent tumor killing activity in humans, but cytokine release related toxicities and relatively shorter half-lives have limited their clinical utility.

HBM7020 is a novel BCMA x CD3 bispecific antibody generated with our state-of-the-art **HBICE™** (HCAb-based Bispecific Immune Cell Engager) platform. It has one Fab binding to CD3 and two HCAbs (Heavy Chain only monoclonal antibodies) binding to BCMA, which improve its selectivity to BCMA-positive MM cells. HBM7020 is a highly efficacious BsAb to selectively deplete BCMA-positive MM cells with limited cytokine release and represents a novel therapeutic alternative for MM patients and other BCMA overexpressing tumors.

HBICE™ and HBM7020

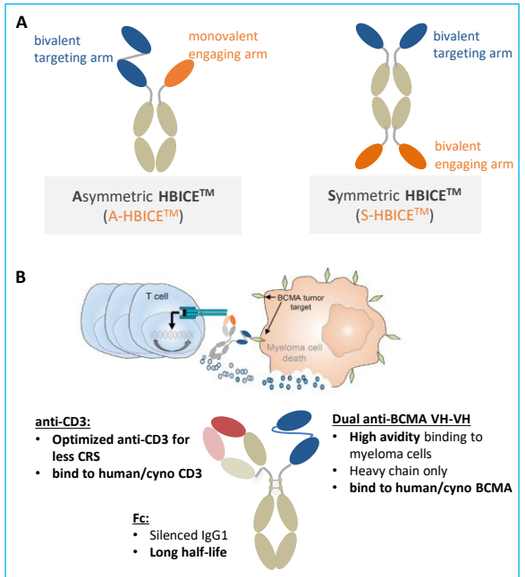
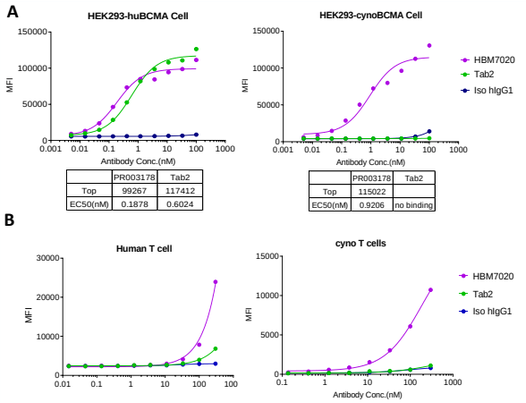


Figure 1: HBM7020 design and mode of action
A. HBICE™ platform. B. HBM7020 is composed of one Fab binding to CD3, two HCAbs binding to BCMA, and the silenced human IgG1.

Key Results

- ✓ **HBM7020, a novel BCMAxCD3 BsAb generated with our HBICE™ platform cross reacts with human & cyno BCMA/CD3**
- ✓ **HBM7020 is highly efficacious in selectively depleting BCMA-positive MM cells with limited cytokine release**
- ✓ **The activity of HBM7020 was not impacted by the presence of soluble BCMA , APRIL and BAFF.**
- ✓ **With a half-life of 4 days HBM7020 showed robust tumor growth inhibition and complete tumor clearance in a NCI-H929 xenograft model with SC administration of 0.5mg/kg each week (QW).**

Binding Activity



	PR003178	Tab2
Top	99267	117412
EC50(nM)	0.1878	0.6024

	PR003178	Tab2
Top	115022	
EC50(nM)	0.9206	no binding

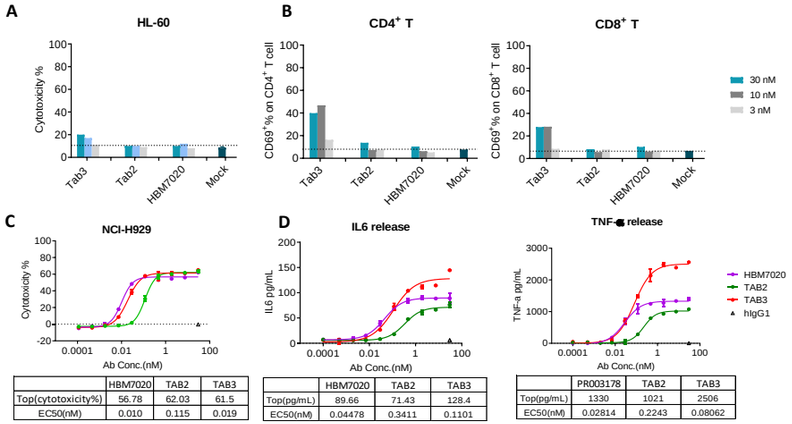
C Optimized anti-CD3 affinity

Cytokine release

	HBM_medium	**HBM7020**	HBM_weak	TAB2(TNB)	TAB3(AMG)
EC50(nM)	~100nM	Very weak (>100nM)	Very weak (uM)	Very weak (uM)	11.5

Figure 2: HBM7020 binding activity to human and cyno BCMA and CD3
A. HBM7020 has high affinity to human and cyno BCMA cell lines. B. HBM7020 has cross reactivity to human and cyno T cells. C. HBM7020 has optimized the anti-CD3 binding affinity.

Selective Targeting BCMA+ Cell *in Vitro*



	HBM7020	TAB2	TAB3
Top(cytotoxicity%)	56.78	62.03	61.5
EC50(nM)	0.010	0.115	0.019

	HBM7020	TAB2	TAB3
Top(pg/mL)	89.66	71.43	128.4
EC50(nM)	0.04478	0.3411	0.1101

	PR003178	TAB2	TAB3
Top(pg/mL)	1330	1021	2506
EC50(nM)	0.02814	0.2243	0.08062

Figure 3: HBM7020 is a highly efficacious BsAb to selectively deplete BCMA-positive MM cells with limited cytokine release. A. HBM7020 shows no off-target killing on BCMA negative cell HL-60 in human PBMC. B. Without target cells, HBM7020 doesn't induce the expression of T cell activation marker (CD69) in primary human T cells. C. HBM7020 induces potent efficacy on NCI-H929 cell by human PBMC in vitro killing. D. IL-6 and TNF-a were measured by ELISA.

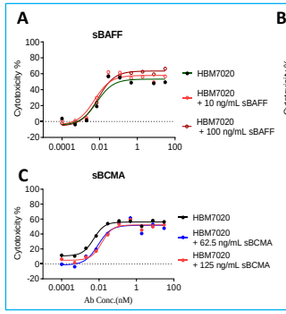


Figure 4: The presence of soluble BCMA and APRIL and BAFF does not affect HBM7020 potency

Tumor Inhibition *In Vivo*

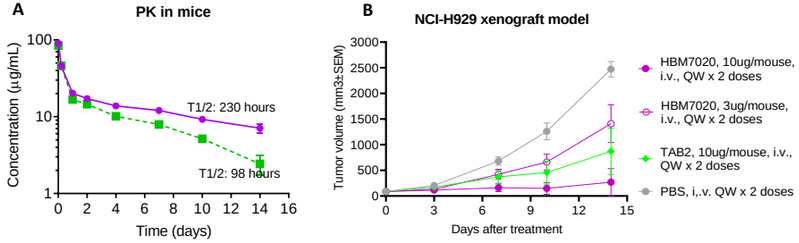


Figure 5: HBM7020 mediates the clearance of BCMA-expressing tumor cells by human PBMC in NSG mice and has long half life in vivo. A. HBM7020 has a half-life 9.5 days in mice test by total antibody method (purple) and 4 days by functional domain method (green). B. HBM7020 drives the robust tumor cell growth inhibition and nearly eradicates tumors at a QW dose 10ug/mouse in the subcutaneous NCI-H929 xenograft model.

Conclusion

Key Parameters	HBM7020	Tab2(TNB)	Tab3(AMG)
Binding on BCMA (cell, EC50 nM)	0.18nM (HEK293-BCMA) / 1.2nM (NCI-H929)	1) 0.6 nM (HEK293-BCMA) / 4.3nM (NCI-H929) 2) Not cross to cyno	116 nM (NCI-H929)
Binding on CD3 (hu T, EC50 nM)	Weak (>100nM)	1) Very weak 2) Not cross to cyno	11.5 nM
In vitro lysis on NCI-H929(EC50)	EC50: 0.01 nM	EC50: 0.115 nM	EC50: 0.019nM
Cytokine release (IL-6, pg/ml)	Max: 89.6 EC50: 0.045 nM	Max: 71.4 EC50: 0.34 nM	Max: 128.4 EC50: 0.11 nM
Cytokine release (TNF-α, pg/ml)	Max: 1330 EC50: 0.028 nM	Max: 1022 EC50: 0.22 nM	Max: 2506 EC50: 0.081nM
In vivo efficacy	89% (0.5mpk)	64% (0.5mpk)	N.D
pK in mice	~ 4 days	~8 days	N.D

Highlights

- ➢ **A novel BCMAxCD3 BsAb generated using the HBICE™ platform with a "2+1" format renders strong cooperative binding to BCMA**
- ➢ **Cross reactive to both human and cyno BCMA/CD3**
- ➢ **Potent tumor killing efficacy and favorable safety profile due to optimized CD3 affinity to minimize cytokine storm**
- ➢ **Excellent PK/PD profile and impressive biophysical properties support further pre-clinical development – IND planned for Q1/2021**

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