HBM1007 – A Highly Potent Anti-CD73 mAb Candidate For Mono And Combination IO Therapy

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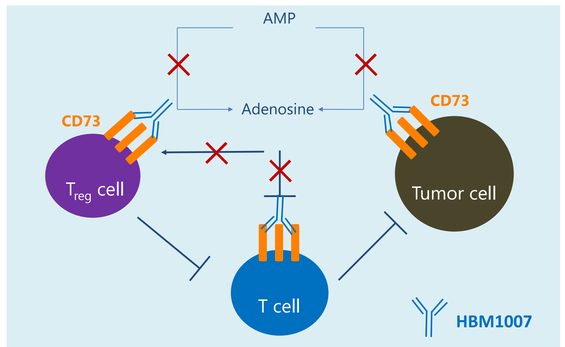
Abstract

CD73, an ecto-5'-nucleotidase, plays a major role in de-phosphorylation of the extracellular adenosine monophosphate (AMP) to adenosine, which in turn is a potent immunosuppressive metabolite that modulates the immune reaction within the tumor microenvironment (TME). High concentration of adenosine, predominantly signaling through the A2A receptor, suppress innate and adaptive immune cell responses leading to tumor escape from immune surveillance. Recent studies have shown a significant overexpression of CD73 in solid tumors alongside it's functional upregulation by inflammatory mediators and hypoxia. Thus, inhibition of CD73 enzymatic activity and its surface expression in the TME may improve anti-tumor immune activity.

To test this hypothesis, we designed and developed a fully human monoclonal antibody with unique structure to recognize CD73. This antibody works through a dual mode of action, 1) it can block the enzymatic activity of both membrane and soluble CD73 independent on AMP concentration, suggesting its sustainable activity in TME, and 2) it reduces the surface expression of CD73. As a result, both enzymatic and non-enzymatic dependent functions of CD73 were significantly reduced. *In vitro* and *in vivo* testing demonstrates a superior anti-tumor activity over reference antibodies.

Our findings reveal a promising candidate as an effective therapy for patients with high levels of CD73 expression. An even broader patient population that even may benefit from this unique dual mechanism of action of CD73-targeting antibody in a further combination therapy.

Mode of Action



Key Points

- HBM1007-1 shows sustained CD73 enzymatic blockade activity and high potency to both cell-surface and soluble CD73 resulting from its unique allosteric properties.
- HBM1007-1 shows compelling results in downregulating cell-surface expression of CD73 on tumor cells.
- Significant anti-tumor efficacy in preclinical models expressing CD73 highlight potential applications of HBM1007-1 in patients with high expression levels of CD73.

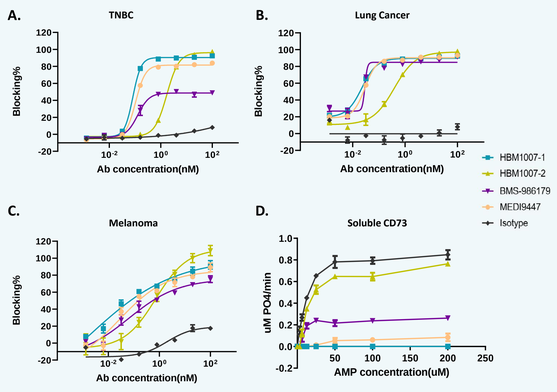
Results

High Binding Affinities of HBM1007-1 to Human/Cyno CD73

Antigens	ka (1/Ms)	kd (1/s)	KD (M)
Human CD73	1.5×10^{6}	3.8×10^{-5}	2.5×10^{-11}
Cyno CD73	2.2×10^{6}	9.0×10^{5}	4.2×10^{-11}

Binding affinity of HBM1007-1 to human/cyno CD73 proteins by BiaCore

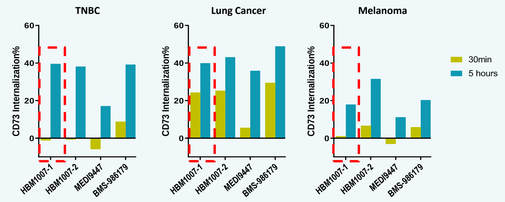
HBM1007-1 Blocks CD73 Enzymatic Activity



HBM1007 mAbs block CD73 enzymatic activity in (A, B, C) tumor cell lines, and (D) soluble CD73

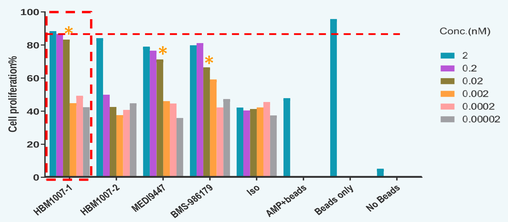
Results

HBM1007-1 Downregulates Surface CD73



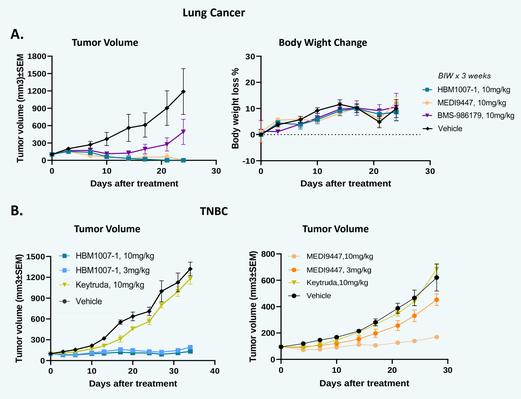
HBM1007 mAbs downregulate surface CD73 on human cancer cells by internalization

HBM1007-1 Recovers Primary T Proliferation



HBM1007 mAbs block AMP inhibition on primary T cell proliferation

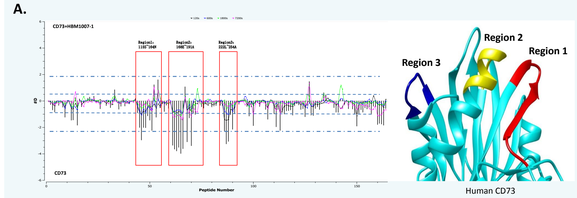
HBM1007-1 Reduces Tumor Growth



HBM1007-1 reduces tumor growth in human PBMC injected (A) lung cancer (B) TNBC models.

Binding Epitopes of HBM1007-1

A.



B.

HDX region 1	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146
>P21589	Y	L	P	Y	K	V	L	P	V	G	D	E	V	V	G
Ala scanning(A)															

HDX region 2	182	183	184	185	186	187	188	189
>P21589	K	T	L	N	V	N	K	I
Ala scanning(A)								

HDX region 3	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254
>P21589	I	V	T	S	D	D	G	R	K	V	P	V	V	Q	A
Ala scanning(A)															

Note: Residues in red are CD73 epitopes reducing binding to HBM1007-1 after alanine mutation.

(A) HDX result (B) Alanine scanning result

Conclusions

- ✓ HBM1007-1, generated from the H2L2 Harbour Mice®, is a fully human monoclonal antibody that shows high potency to irreversibly block both cell-surface and soluble CD73 enzymatic activity.
- ✓ It downregulates CD73 surface expression notably by internalization and potently recovers primary T cell proliferation.
- ✓ HBM1007-1 may significantly enhance anti-tumor immune responses both in monotherapy as well as potential combination therapy in clinical setting.

Contacts

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