987P A novel therapeutic antibody against CD73 that ameliorates the tumor microenvironment and improves the efficacy of cancer immunotherapy.

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Introduction

CD73 is expressed on certain types of leukocytes and tumor cells and is known as a poor prognostic factor in several cancers. CD73 catalyzes conversion of extracellular adenosine monophosphate (AMP) to adenosine (Ado) which accumulates in the tumor microenvironment (TME). Ado suppresses immune activation through Ado receptors on several immune cells, allowing tumors to escape from the immune surveillance. Therefore, inhibition of CD73 activity provokes T cell activation and reverses immune suppression exerted by Ado. Thus, our novel potent anti-CD73 antibody (BP1200_002) is expected to do provide cancer immunotherapy options.

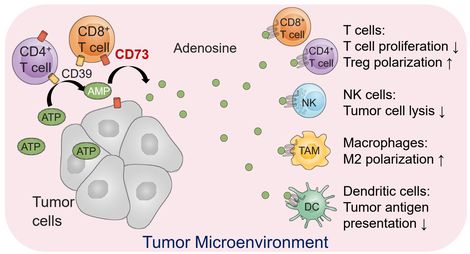
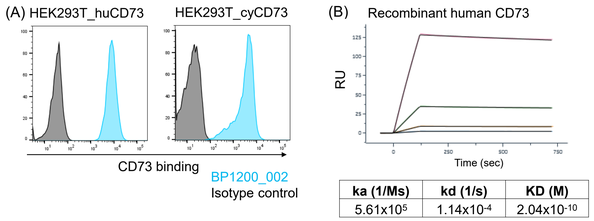


Figure 1. Ado is generated by CD39 and CD73 suppresses immune cells, such as T cells, NK cells, macrophages and dendritic cells in TME.

Result

BP1200 binds human and cynomolgus CD73 with high affinity.



ka (1/Ms)	kd (1/s)	KD (M)
$5.61x10^{5}$	$1.14x10^{-4}$	$2.04x10^{-10}$

Figure 2. Binding of BP1200_002 to human and cynomolgus CD73 (A) and the kinetics against recombinant human CD73 (B).

BP1200 inhibits the activities of CD73 on cell membrane and soluble CD73 without hook effect.

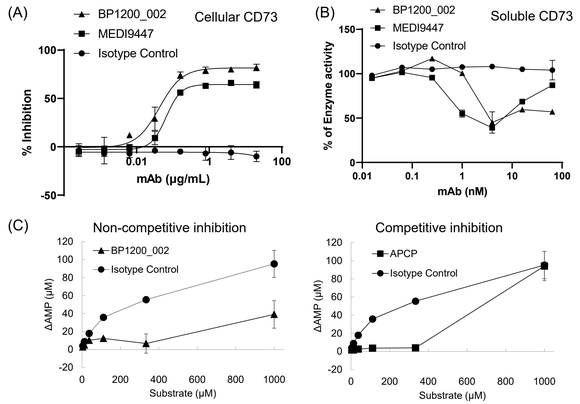


Figure 3. Inhibition of cellular CD73 (A) and soluble CD73 without hook effect (B). BP1200_002 is a non-competitive inhibitor of CD73 (C). MEDI9447 is in-house produced analogues. Adenosine 5'-(α,β-methylene) diphosphate (APCP) is a CD73 small molecule inhibitor.

BP1200 internalizes into cells and depletes CD73 on cell surface.

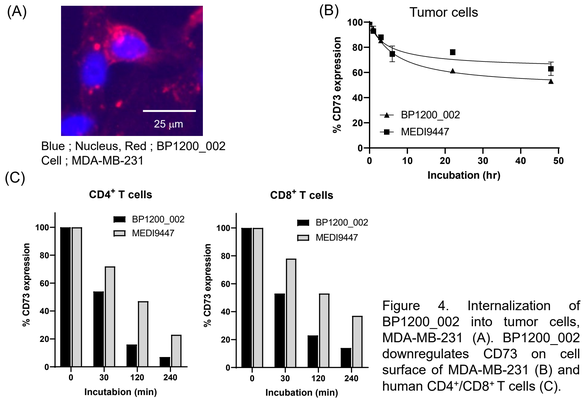


Figure 4. Internalization of BP1200_002 into tumor cells, MDA-MB-231 (A). BP1200_002 downregulates CD73 on cell surface of MDA-MB-231 (B) and human $CD4^{+}$/$CD8^{+}$ T cells (C).

BP1200 enhances T cell proliferation and cytokine production.

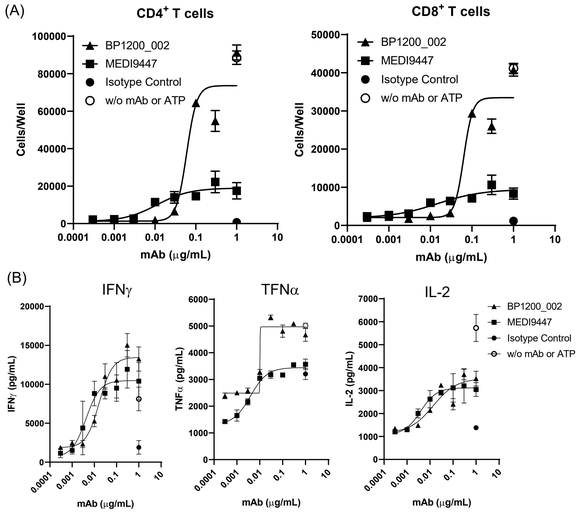


Figure 5. Human $CD4^{+}$ and $CD8^{+}$ T cells were stimulated with anti-CD3/CD28 beads in the presence of ATP. BP1200_002 enhanced both proliferation of T cells (A) and production of cytokines (B).

BP1200 augments the cytotoxicity of T cells.

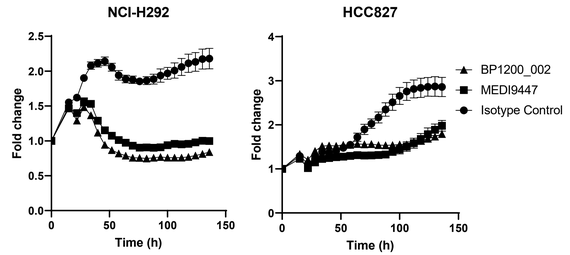


Figure 6. Augmentation of PBMCs-mediated cytotoxicity against tumor cells by BP1200_002 in the presence of ATP. Data are presented as means ±SEM. Both NCI-H292 and HCC827 are human lung cancer cell line.

BP1200 inhibits tumor growth in combination with immune checkpoint blockades.

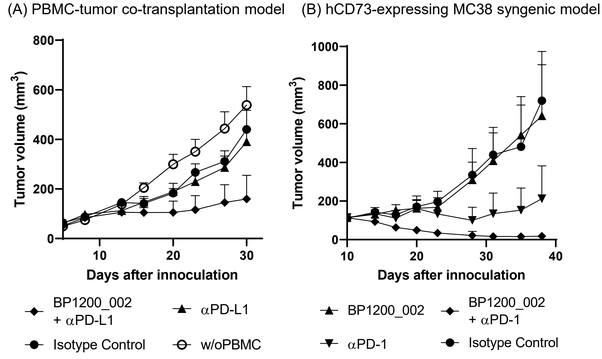


Figure 7. Effects of BP1200_002 in combination with PD-1 blockers on tumor growth in mice. (A) NOD mice were transplanted with human PBMC and NCI-H292 cancer cell line, then treated by BP1200_002 (0.2 mg/body, BIW) in combination with anti-PD-L1 antibody (0.2 mg/body, BIW). (B) B6 mice were transplanted with MC-38 expressing hCD73, then treated by BP1200_002 (10 mg/kg, BIW) in combination with anti-PD-1 (3 mg/kg, QW) . Data are presented as means ±SEM.

Conclusion

- BP1200_002 is a humanized anti-CD73 antibody that attenuates the AMP hydrolysis activity of CD73 as a non-competitive inhibitor without hook effect.
- BP1200_002 is internalized into tumor and T cells and results in the downregulation of CD73 expression on the cell surface.
- BP1200_002 enhances the proliferation, cytotoxicity, and cytokine production of T cells under the TME condition.
- The combination of BP1200_002 and immunocheckpoint antibody for cancer treatment will be a promising regimen in clinical practice.

Disclosure

T. Obonai: Employee of BrightPath Biotherapeutics

BrightPath Biotherapeutics