Preclinical development of humanized CD39 (IPH52) and CD73 (IPH53) blocking antibodies targeting the ATP/Adenosine immune checkpoint pathway for cancer immunotherapy

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Abstract

The immunosuppressive role of CD39, expressed on both Tregs and tumor cells, has been largely demonstrated. CD39 expression in the tumor environment has been associated with poor disease outcome and/or with a pro-metastatic phenotype. Blockade of CD39 and CD73 may promote anti-tumor immunity by reducing adenosine (A) accumulation and increasing levels of ATP, which possesses immunostimulatory properties.

Blockade of CD73 enzymatic activity has recently been reported to improve immune checkpoint inhibitor anti-tumor activity. In addition, we show that in vivo blockade of ATP/adenosine pathway in CD39 KO mice resulted in improved anti-tumor efficacy of immunotherapy-based therapies (i.e. PD-1, CTLA-4) and chemotherapy such as Oxaliplatin.

Immunohistochemistry (IHC) and flow cytometry staining showed that CD73 is rather expressed by tumor cells and that CD39 is frequently up-regulated on tumor infiltrating lymphocytes (TILs) compared to PBMC or adjacent non-tumor tissue.

We have generated human anti-CD39 (IPH52) and anti-human CD73 (IPH53) blocking antibodies (Abs) with unique properties for cancer immunotherapy. These Abs potentially inhibit the enzymatic activity of both the soluble and membrane-associated forms of their respective target. Both Abs efficiently reverse adenosine-mediated T cell suppression in vitro in presence of ATP and CD39- and CD73-expressing immune cells. The anti-CD39 PH52 Ab enhances dendritic cells (DC) activation and subsequent T cell proliferation in vitro, probably by maintaining high concentrations of ATP in the extracellular compartment. The anti-CD39 IPH52 Ab is more potent than benchmark Abs currently in phase I clinical development for the blockade of soluble and membrane-associated CD73 enzymatic activity and for AMP-mediated T cell suppression reversal. Firstly, we showed that combining IPH52 and IPH53 Abs at sub-optimal doses leads to a strong reversion of immune cell inhibition in the presence of the ATP.

Taken together, these data support the rationale for clinical development of anti-CD39 and anti-CD73 neutralizing Abs for cancer immunotherapy, potentially in combination with chemotherapy or immune checkpoint blockade.

1. Deletion of CD39 in vivo improves anti-tumor efficacy of immune checkpoint blockade and chemotherapies

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2. In human tumors CD39 is mostly upregulated on tumor infiltrated lymphocytes

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3. In human tumors CD73 is rather expressed on tumor cells

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4. IPH52 (CD39) and IPH53 (CD73) Abs block enzymatic activity of both membrane-bound and soluble CD39 and CD73

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5. IPH52 and IPH53 blocking Abs reverse Ado-mediated T cell suppression

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6. IPH52 enhances ATP-mediated DC activation and resulting T cell proliferation

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7. Combined CD39 and CD73 blockade strongly reverses Ado-mediated T cell suppression

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Conclusion

- **IPH52 (anti-CD39 Ab)**
  - Humanized Fc-silent IgG1 antibody, blocking membrane and soluble CD39
  - Anti-CD39 blocking mAb allows (i) to sustain extracellular ATP that promotes immune responses and (ii) to block the generation of adenosine that is immunosuppressive

- **IPH53 (anti-CD73 Ab)**
  - Humanized Fc-silent IgG1 antibody, blocking membrane and soluble CD73
  - Differentiated and superior in vitro activity compared to MEDI and BMS CD73 blocking Abs
  - IPH52/IPH53 combination
  - In vitro synergy in T cell suppression assay