Inhibition of CD39 by AB598 Increases Extracellular ATP Resulting in Activation of Myeloid Cells and T Cells to Enhance Anti-Tumor Immunity

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Introduction

Figure 1 presents a schematic representation of the proposed mechanism of action for AB598. AB598 potently inhibits CD39 (encoded by the ENTPD1 gene), a transmembrane ecto-5’-nucleotidase. By depleting extracellular ATP, AB598 may enhance T cell activation and cytokine production, potentially leading to increased anti-tumor immunity.

AB598-mediated inhibition of CD39 results in an increase in ATP concentrations in the extracellular milieu, which can activate myeloid cells through the P2X7 receptor. This activation can promote the release of pro-inflammatory cytokines and chemokines, enhancing the recruitment and activation of effector T cells. In addition, AB598 treatment may also lead to the release of immunostimulatory antigens, further augmenting the immune response.

Results

AB598 inhibits CD39 enzymatic activity in dissociated tumor cells

Figure 2 A: Inhibition of CD39 enzymatic activity by AB598 in dissociated tumor cells. The enzymatic activity of CD39 was measured using the enzyme-linked immunosorbent assay (ELISA) method. AB598 treatment resulted in a significant decrease in CD39 enzymatic activity compared to the control group.

Figure 2 B: Time course analysis of AB598-mediated inhibition of CD39 enzymatic activity. The enzymatic activity of CD39 was measured at different time points after AB598 treatment. A significant decrease in enzymatic activity was observed over time.

AB598 boosts the effect of chemotherapy to promote moDC maturation and activity

Figure 3: AB598 potently enhances the effect of chemotherapy to promote moDC maturation and activity. (A) AB598 boosts the effect of chemotherapy to promote moDC maturation and activity. The expression of MO1 and CD83 markers was assessed by flow cytometry. (B) Statistical analysis of the results. AB598 treatment resulted in a significant increase in MO1 and CD83 expression compared to the control group.

In the presence of ADP-Induced Immunosuppression, Combining AB598 and Etruma Results in More Effective T Cell Activation

Figure 4: Combination of AB598 and Etuma results in enhanced T cell activation and cytokine secretion. (A) Schematic representation of the experimental setup. (B) Flow cytometry analysis of CD39 expression on T cells. AB598 treatment resulted in a significant increase in CD39 expression compared to the control group.

Conclusions

AB598 potently inhibits CD39, the extracellular ATPase mediating ATP degradation in the tumor microenvironment. Treatment of cancer cells with chemotherapy induces T cell activation, which is further enhanced by AB598 treatment. The combination of AB598 and Etuma results in more effective T cell activation and cytokine secretion, leading to improved anti-tumor immunity. These findings support the potential clinical application of AB598 as an adjuvant therapy in cancer immunotherapy.