AB598, a Therapeutic Anti-CD39 Antibody, Elevates ATP and Increases Immunogenicity in the Tumor Microenvironment

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INTRODUCTION

AB598, an IgG1 anti-CD39 antibody that blocks CD39 (ENTPD1) enzymatic activity, is being developed as a novel cancer immunotherapy. CD39 is highly expressed on immune and stromal cells within the tumor microenvironment (TME) and is responsible for the conversion of adenosine triphosphate (ATP) into adenosine monophosphate (AMP). Therapeutic hypothesis: AB598 can bind and inhibit CD39 activity on immune cells, leading to an increase in local levels of immunostimulatory ATP. In the TME, elevated ATP exerts its effect by signaling through members of the P2X and P2Y purinergic receptor families.

RESULTS

High CD39 Expression Across Primary Dendritic Cell Subsets and in in vitro-derived Dendritic Cell and Macrophage Subsets

In vitro-Derived Macrophages Express Highest Levels of CD39

AB598 Promotes ATP-Dependent Dendritic Cell Maturation and Macrophage Inflammation Activation

Conclusions

CD39 is expressed at both the mRNA and protein level, on both primary and in vitro-derived myeloid cell populations.

- Neutralizing profiling confirms CD10 expression and the presence of TLR, CD3, CD68, and CD206 across myeloid cell profiles, indicating the presence of necessary components for ATP-induced anti-tumor immunity driven by dendritic cells and inflammation activation.
- P2Y7 and P2Y11 have complementary expression patterns, which are supported by the finding that P2Y11 antagonism, but not P2Y7 antagonism, affects ATP-driven INDIC induction in macrophages.
- Increases in CD83 and CD206, indicative of macrophage maturation, and IL-1β and IL-18 secretion, indicative of inflammation activation, are ATP-dependent, a pattern which is amplified in the presence of the Arcus CD20 inhibitory antibody, AB598.

Several solid tumor types express the machinery needed to respond to CD39 inhibition.

- Several common, chemotherapeutic agents are immunogenic, cell death (CD53 induction and release ATP during cell death. CD39 inhibition by AB598 prevents the degradation of ATP) leading to higher nonselective concentrations of immunostimulatory ATP.

- Taken together, AB598 can amplify the effects of CD inhibitor chemotherapy to enhance myeloid cell activation, boosting anti-tumor immunity in solid tumors.

CONTACT

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