Reversal of Adenosine-Mediated Immune Suppression by AB421, a Potent and Selective Small-Molecule CD73 Inhibitor


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AB421 RESTORES α–PD-L1 MEDIATED ENHANCED T CELL ACTIVATION IN THE PRESENCE OF AMP

CD73 is HIGHLY EXPRESSED IN MULTIPLE TUMORS ACROSS DIFFERENT CELL TYPES

ADMINISTRATION OF AB421 ELEVATES AMP-TO-ADENOSINE RATIO

Conclusions:

- We have designed a highly potent and selective small-molecule CD73 inhibitor, AB421, which inhibits endogenous and reversible CD73 activity in human CD8+ and CD4+ T cells with IC50 values of 4.5 pM and 6.2 pM, respectively.
- Mechanistically, addition of AMP repressed expression of activation markers (CD25) and immune checkpoint proteins (CTLA-4, PD-1, TIM-3, LAG-3, ICOS, CD28) in the MLR assay. This suggests that activation of the adenosinergic pathway on T cells is dominant and may limit the utility of most therapeutic antibodies targeting immune checkpoint proteins by curtailing their expression and/or upregulation (as was seen with an α-PD-L1 mAb and AMP co-culture systems).
- Analysis of TCGA database, tumor microarrays, and flow cytometry showed differential expression of CD73 across tumor types.
- Finally, we show that AB421 can elevate AMP to ADO ratios in vivo in a dose-dependent manner, reflecting systemic inhibition of CD73.

AB422 Limits the Inhibitory Effect of AMP on CD4+ and CD8+ T cell Activation

OPPOSING EFFECTS OF AMP AND α–PD-L1 ON CO-INHIBITORY AND CO-STIMULATORY PROTEIN EXPRESSION

Expression of indicated proteins in the presence of AMP (top row) or α–PD-L1 antibody (bottom row) compared to control samples were determined by flow cytometry. Each color represents one donor.