The Dual A2aR/A2bR Antagonist AB928 Reverses Adenosine-Mediated Immune Suppression and Inhibits Tumor Growth in vivo


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Introduction

High levels of immunosuppressive adenosine are found in the tumor microenvironment, reaching 50-100 µM in experimental models. Adenosine exerts its effects on immune cells primarily through the adenosine receptors A2aR and A2bR, which increase intracellular levels of cAMP, leading to CREB phosphorylation (pCREB). We have previously shown that the dual A2aR/ A2bR antagonist AB928 is capable of inhibiting adenosine-induced pCREB in healthy human volunteer (HV) blood lymphocytes. AB928 has also been shown to relieve adenosine-mediated T cell suppression in vitro and exhibit combinatorial effects with standard of care chemotherapeutics in mouse syngeneic tumor models. Herein, we show that AB928 is capable of inhibiting NECA-induced gene expression changes and CREB phosphorylation in non-small cell lung carcinoma (NSCLC) primary human tumor cells. Additionally, observations from our in vitro human studies showing the combinatorial effect of AB928 and α-PD-1 were reproduced in B16F10 syngeneic tumors.

Methods

Adenosine was utilized to suppress the activation of primary human immune cells +/- AB928. Human WB was stimulated with 5 µM of NECA and flow cytometry was used to quantify AB928-mediated inhibition of pCREB and CD3ζ phosphorylation. NanoString analysis was performed on human whole blood RNA using the nCounter Human Immune Profiling panel v2. Established B16F10 tumors were treated with α-PD-1 +/- AB928 and gene expression was determined from excised mouse tumors using the nCounter PanCancer immune profiling panel.

AB928 Reverses Adenosine-Mediated Immunosuppression

AB928 Reverses NECA Induced Gene Expression Changes in Whole Blood

AB928 Rescues NECA Mediated Suppression of CD3ζ Phosphorylation

Conclusions

- AB928 restores adenosine/NECA mediated suppression of cell activation, signaling events, and gene expression in vitro.
- AB928 shows anti-tumor activity as both a single agent and in combination with α-PD-1 therapy in vivo.
- AB928 is currently being tested in clinical trials in combination with either standard of care chemotherapy or α-PD-1.