Combining adenosine receptor inhibition, with AB928, and chemotherapy results in greater immune activation and tumor control

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Abstract

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Introducing

In many tumors, extracellular adenosine contributes to an immunosuppressive Tumor Micro-Environment (TME) via activation of the A₂A receptor, expressed on lymphocytes, and the A₃ receptor, expressed on myeloid cells. Relative to other tissues like the brain, adenosine concentrations in the TME are much higher. Tumors also contain higher levels (7% of albumin, to which many drugs bind non-specifically.

Methods

Human Immune Cell Assays: CD4+ or CD8+ T cells were isolated from PBMC using RosetteSep separation and were stimulated with CD2/CD3/CD28 microbeads +/- adenosine/Ehha -/- AB928. Human CD4+ cells were differentiated into mDC for 6 days in IL-4/OM-CSF +/- adenosine/Ehha +/- AB928. Adenosine was present during mDC activation via iNKT or LPS. Cells were washed in excess buffer, to remove residual adenosine, prior to setting up the mixed leukocyte reaction (MLR). Supernatants were collected 4 days after initiation of the mDC/iNKT-culture.

Mouse Tumor Models: Female C57Bl/6 mice (Jackson labs) were inoculated with either AT-3-OVA (gifted from the lab of Mark Smyth, QIMR Australia) or MC38. Mice with established tumors were dosed with chemotherapy +/- AB928 (100 mg/kg PO Bid).

AB928 Whole Blood Potency

Target IC₅₀ (nM)

CD8 pCREB (against 5 µM NECA) 87.7 ± 54 nM (n = 26)

Adenosine Receptor Expression on Human Immune Cells

CD73 Expression on Human Tumors and Tumor Infiltrating Immune Cells

Adenosine mediated Suppression of T Cell Activation is Blocked by AB928

Adenosine Impairs Dendritic Cell Maturation, Decreases T Cell Recruiting Chemokines & Increases Those Linked to MDSC Recruitment

AB928 Inhibits Adenosine-Receptor Mediated Increases in pCREB

Ab928 In Combination with Either Doxorubicin or Oxaliplatin Results in Greater Tumor Control

Conclusions

- A₂A receptor is enriched on T and NK cells
- Human myeloid cells express both A₂A and A₃R
- Adenosine receptor activation on T cells results in increased activation, and on myelocytes blunts their ability to stimulate T cells
- AB928 inhibits adenosine-mediated immune suppression
- In combination with chemotherapy, AB928 results in greater tumor control in multiple mouse tumor models
- AB928 is expected to enter clinical trials in combination with standard of care chemotherapy in 2018