# A novel non-competitive and non-brain penetrant adenosine $A_{2A}$ receptor antagonist designed to reverse adenosine-mediated suppression of anti-tumor immunity

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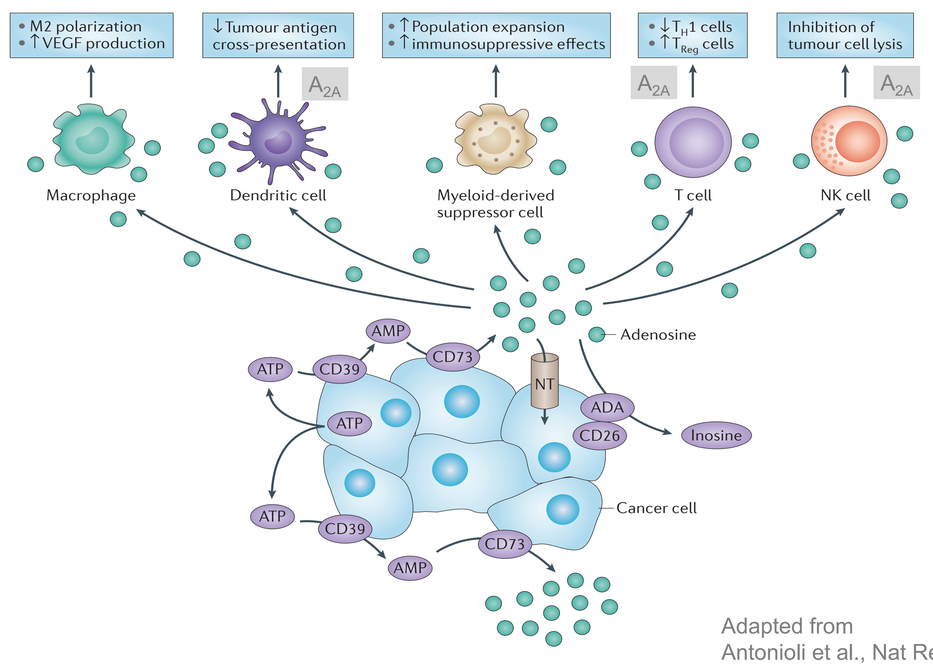
## SUMMARY

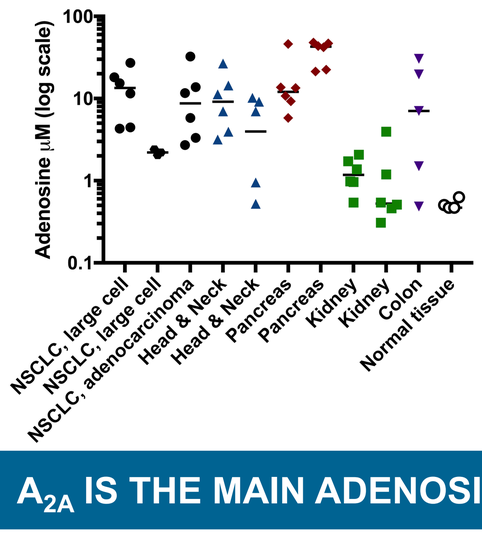

- High levels of extracellular adenosine drive tumor immunosuppression
- Adenosine concentrations in tumors are at least 10-fold higher compared to normal tissue
- $A_{2A}$ is the most prevalent adenosine receptor of immune cells
- Adenosine suppresses innate and adaptive immune reactions via signaling through $A_{2A}$
- $A_{2A}$ antagonists repurposed from Parkinson's disease dramatically loose potency in a high adenosine environment
- iTeos $A_{2A}$ antagonist is designed for immuno-oncology:
  - ✓ Non-competitive and selective inhibitor of $A_{2A}$
  - ✓ Highly potent in high intratumoral adenosine concentrations
  - ✓ Non-brain penetrant, avoiding potential CNS side-effects at doses needed to inhibit tumoral A2A
  - ✓ Rescues adenosine-driven T cell and innate cell immunosuppression
  - ✓ Increases *in vivo* anti-tumor efficacy of a-CTLA4 and a-PD1


## ADENOSINE-DRIVEN IMMUNOSUPPRESSION



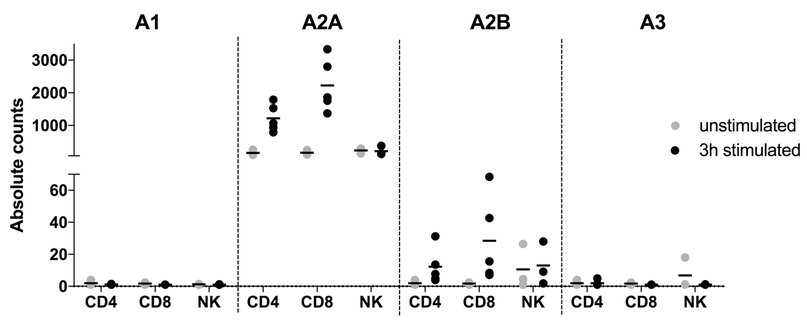

Adapted from
Antonioli et al., Nat Rev Cancer 2013

## HIGH EXTRACELLULAR ADENOSINE CONCENTRATION IN TUMORS




**Adenosine concentrations in patient-derived xenografts.** Extracellular adenosine content was measured in 10 PDX from the indicated tumor histological types and normal tissue. Extracellular fluid from the PDX was obtained by microdialysis and adenosine was quantified by LC-MS. The mean adenosine concentration was 10,71 ± 1,70 µM (SEM) (n = 5 to 6 tumors/PDX model).

## $A_{2A}$ IS THE MAIN ADENOSINE RECEPTOR IN IMMUNE CELLS

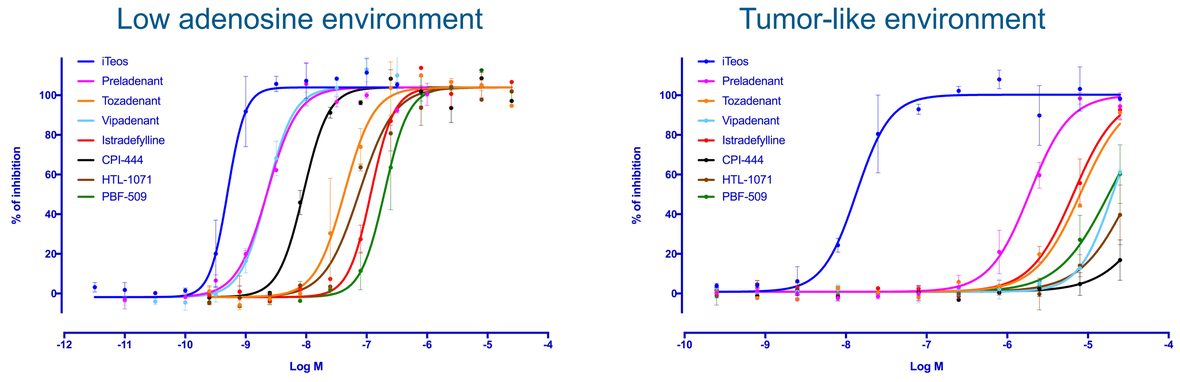



mRNA quantitation by Nanostring nCounter technology.

## ITEOS $A_{2A}$ ANTAGONIST IS POTENT, SELECTIVE AND NON-BRAIN PENETRANT

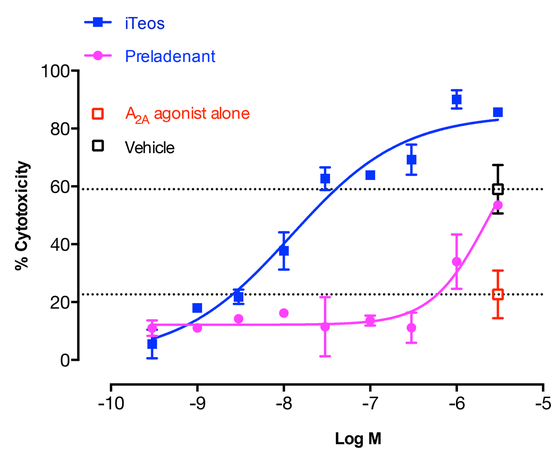
| Parameter | iTeos $A_{2A}$ antagonist |
|---|---|
| Potency (cAMP, $IC_{50}$) | 0.6 nM |
| Potency in high adenosine (cAMP, $IC_{50}$) | 26 nM |
| Potency in whole blood vs 25 µM CGS-21680 (pCREB, $IC_{50}$) | 0.9 nM |
| Selectivity vs other adenosine receptors | > 1500x vs $hA_1$<br>> 800x vs $hA_{2B}$<br>> 20000x vs $hA_3$ |
| CNS penetration | No |

## ITEOS $A_{2A}$ ANTAGONIST IS HIGHLY POTENT IN THE ADENOSINE RICH TUMOR MICROENVIRONMENT



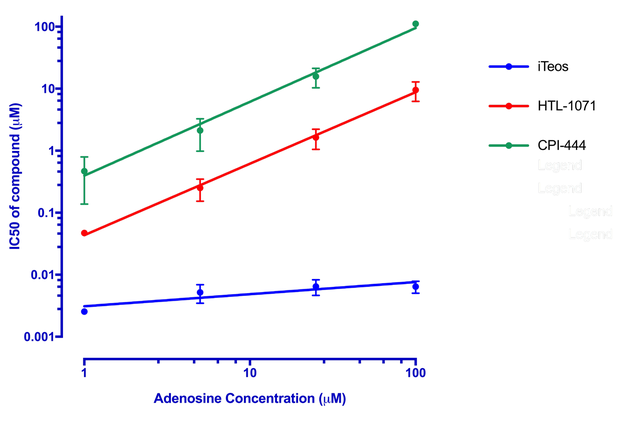

**iTeos $A_{2A}$ antagonist outperforms competitors in normal and adenosine-rich environment**. Stimulation mimics normal (low adenosine) and tumor-like (adenosine-high, 2%HSA) environment, with cAMP used as a readout.

## ITEOS $A_{2A}$ ANTAGONIST INCREASES T CELL CYTOTOXICITY



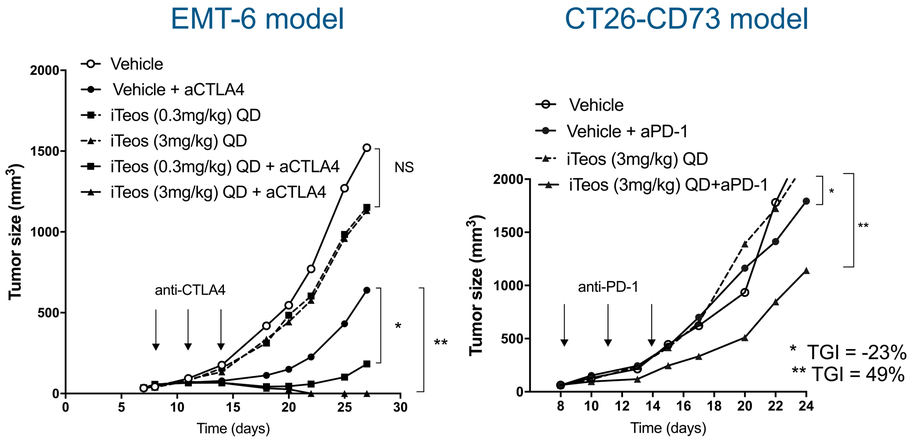

**iTeos compound abrogates $A_{2A}$-mediated inhibition of cytoxicity.** OT1 cells, primed with Ova peptide in the presence of a high concentration of $A_{2A}$ selective agonist and increasing concentrations of iTeos antagonist or Preladenant were then incubated with labeled Ova coated Panc02 cells as target cells.

## ITEOS $A_{2A}$ ANTAGONIST IS A NON-COMPETITIVE INHIBITOR OF $A_{2A}$



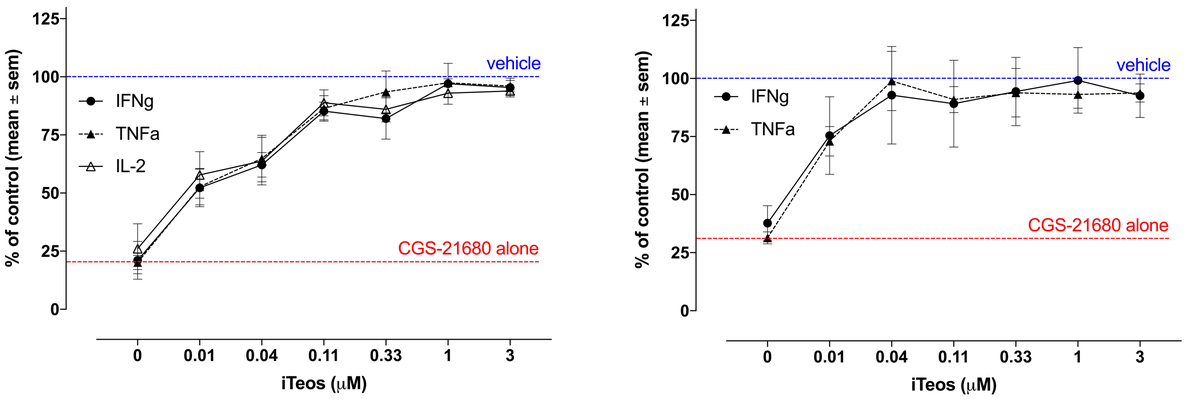

**iTeos $A_{2A}$ antagonist is non-competitive with adenosine.** Human primary CD3 T cells were stimulated with different concentrations of adenosine (+ 2% HSA). cAMP was used as a readout. iTeos compounds are 10-100 times more potent than competitors in low adenosine, and 1000-10000 times more potent at the highest adenosine concentration.

## ITEOS $A_{2A}$ ANTAGONIST INCREASES ANTI-TUMOR EFFICACY OF CHECKPOINT INHIBITORS




**iTeos compound enhances anti-tumor activity of a-CTLA4 and a-PD-1.** The efficacy of iTeos $A_{2A}$ antagonist was evaluated in established EMT-6 and CT26-CD73 syngeneic tumors. Combination of iTeos compound with checkpoint inhibitors resulted in significant tumor growth inhibition (n=9-10 mice/group; * p<0.01, ** p<0.001; TGI was calculated when tumors in vehicle groups reached 1000 $mm^3$).

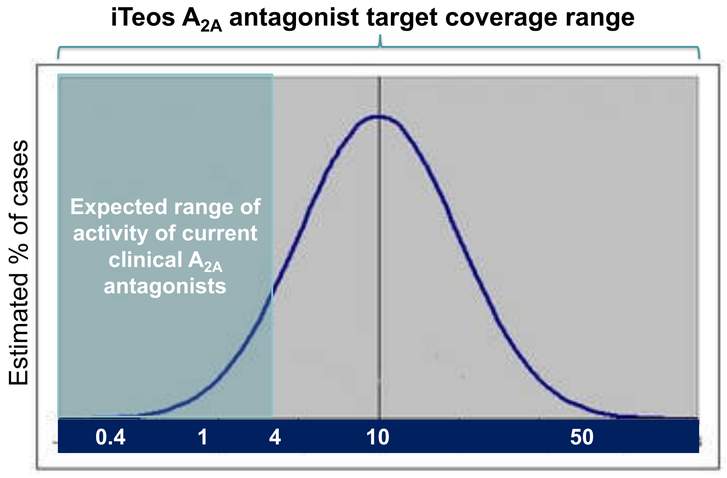
## ITEOS $A_{2A}$ ANTAGONIST INCREASES TH1 CYTOKINE PRODUCTION




**iTeos $A_{2A}$ antagonist restores $A_{2A}$-mediated suppression of T cell and innate cell-derived Th1 cytokines.** Human whole blood was stimulated in the presence of 1 µM of $A_{2A}$ agonist CGS-21680. n = 3 healthy donors.

## CONCLUSIONS

**iTeos $A_{2A}$ antagonist target coverage range**




Distribution of adenosine concentrations in tumors (µM)

**iTeos $A_{2A}$ antagonist is a novel, best-in-class $A_{2A}$ antagonist designed for Immuno-Oncology**

- Non-competitive with adenosine
- Potent in high intratumoral adenosine concentration
- No CNS penetrance
- Reverses adenosine-mediated suppression of cancer immunity, including in high adenosine concentrations found in most human cancers

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