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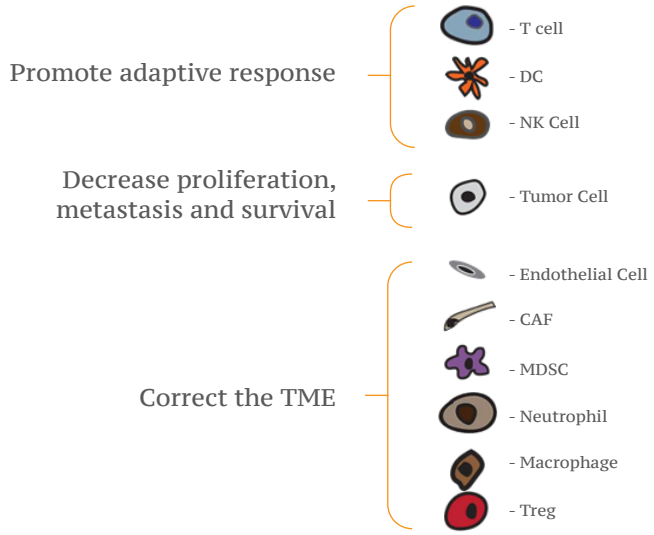
Targeting adenosine to enhance immune response

About the adenosine pathway and receptors

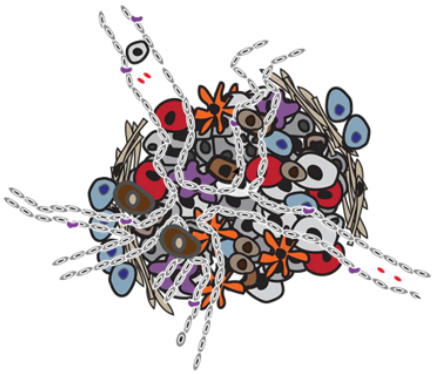
- A critical mechanism of cancer immune evasion is the generation of high levels of immunosuppressive adenosine within the tumor microenvironment (TME).
- Research suggests that the TME has significantly elevated concentrations (100-500-fold) of extracellular adenosine, conferring immunosuppressive and tumor-promoting effects.
- Engagement with adenosine receptors A2A and A2B triggers a dampening effect on the immune response, suppressing effector cell function and stabilizing immunosuppressive regulatory cells.
- Over-expression of A2A and A2B leads to poor prognosis in multiple cancers, including prostate cancer, colorectal cancer and lung adenocarcinoma, driven by a reduced ability to generate an immune response against the tumor (approximately 25-50% of these tumors over express A2A).
- Many cell types in the TME express functional adenosine receptors, making adenosine blockade a promising approach for cancer treatment.

Adenosine: a broad validated target for immunotherapeutic intervention

Leveraging A2A and A2B alone or in combo allows for customization of treatment for given patient/tumor type



Tumor is complex system
Governed by numerous immune cells



Targeting Adenosine in Cancer Immunotherapy to Enhance T-Cell Function; Virgano, et al; Frontiers in Immunology 2019 modified slightly and used under CC BY 4.0

Adenosine antagonists: mechanism of action

- Portage's adenosine antagonists (PORT-6, PORT-7, PORT-8 and PORT-9) can act on multiple immune cell types for more robust immunologic effect

ADAPTIVE IMMUNE SYSTEM

- Promotes an adaptive immune response

TUMOR CELLS

- Decreases tumor proliferation, metastasis and survival

TUMOR MICROENVIRONMENT

- Corrects the TME by removing immunosuppressive activity

Our adenosine inhibitor platform

Portage has the unique ability to evaluate adenosine biology to unlock the best patient populations and best disease settings (oncology and non-oncology) leveraging the adenosine pathway, with four best-in-class or first-in-class oral small molecule inhibitors in development:

PORT-6

Adenosine receptor type 2A (A2A) inhibitor to treat A2A expressing solid tumors

PORT-7

Adenosine receptor type 2B (A2B) inhibitor to treat solid tumors

PORT-8

Dual inhibitor of adenosine receptors 2A and 2B (A2A/A2B) to treat solid tumors

PORT-9

A2B inhibitor to treat colorectal and gastrointestinal cancers, gut-selective

Our adenosine compounds have the potential to be best-in-class as they are more selective, more potent and more durable than other A2A, A2B and dual inhibitors being explored in the space.

Enrichment strategies for clinical trials

Portage is focusing initial efforts on tumor types where other adenosine agents have shown single agent activity. Portage intends to further enrich patients by screening for tumors with high adenosine receptor expression and select for patients that may be more likely to respond and therefore have potential to benefit most from treatment.

Platform synergy

Both Portage's invariant natural killer T cell (iNKT) agonists and adenosine antagonists can potentially act synergistically to break down the barriers of the suppressive tumor microenvironment and stimulate immune cells for more effective treatment. We will continue to evaluate potentially beneficial combinations of our adenosine antagonists and other therapies.

Recent adenosine activity spotlights

The adenosine pathway and tumor escape mechanisms have emerged as a promising area in the field of immuno-oncology. Some of the recent positive data that validates the space includes:

- Blocking adenosine A2B receptors reduces immunosuppression of the tumor microenvironment, reactivating the immune system to increase lymphocyte infiltration, resulting in significant tumor remission.
- Blocking adenosine A2A receptors enabled tumor regression, disease control and survival in refractory renal cell cancer patients
- A2B signaling has been recognized as a major pathway contributing to cancer cell proliferation and growth, angiogenesis, metastasis and immune suppression
- High concentrations of adenosine in the TME are shown to promote tumor growth and broadly suppress protective immunity.

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