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"Forodesine has anticancer immunomodulatory properties through the adenosine pathway"

Adenosine is an immunosuppressive metabolite that is overproduced in the tumor microenvironment and a major player in tumor-induced immunosuppression. Work from our group has contributed to show that adenosine binding to the Adenosine A2A Receptor (A2AR) suppresses CD8 T cell function and activation in the tumor microenvironment, whereas blocking A2AR restimulates anticancer CD8 T cell responses. In this study, I aimed to identify novel therapeutics that can block A2AR signaling, thus restoring CD8 T cell anticancer function. Using molecular docking modeling, I have found that the nucleoside analog forodesine binds to A2AR with a similar ∆G and similar binding residues as adenosine. I tested forodesine in primary CD8 T-cells against an adenosine agonist and measured functional markers associated with T-cell activation and A2AR signaling. I found that forodesine rescues CD8 T-cell activation by binding to A2AR and counteracting adenosine-mediated immunosuppression. I also tested forodesine in highly immunosuppressive Triple-Negative Breast Cancer (TNBC) mouse models and found that forodesine reduces tumor growth via stimulation of CD8 T-cell responses. Based on our findings, nucleoside analogs, like forodesine, could be investigated as novel Immunotherapeutics to successfully stimulate T-cell responses against cancer.