PHARMACOLOGIC INHIBITION OF DGKα ACTIVATES T CELLS AND ENHANCES ANTI-TUMOR IMMUNITY

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Background Immunotherapies blocking checkpoint receptors on T cells have demonstrated impressive activity in cancer patients, however, a significant population of patients do not respond to these therapies or develop acquired resistance over time. Therefore, alternate approaches to enhance T cell immunity are needed to broaden and deepen the current clinical response rates in patients. A potential promising approach is to target intracellular negative regulators of T cell receptor (TCR) signaling. Diacylglycerol (DAG) is a key second messenger that links TCR signal strength to the intensity and duration of signaling by the RAS-extracellular signal-regulated kinase (ERK)- and protein kinase C (PKC)-dependent pathways. Diacylglycerol kinase α (DGKα) is an intracellular lipid kinase that is enriched in T cells and functions as a key negative regulator of TCR signaling by catalyzing the conversion of DAG to phosphatidic acid (PA), thus attenuating DAG-mediated signaling. Inhibition of DGKα maintains levels of DAG following TCR stimulation and potentiates T cell activation. Here we describe a potential first-in-class, potent, highly selective and orally bioavailable inhibitor of DGKα.

Methods The proximal activity and specificity of Gilead’s inhibitor for enhancing the main TCR-driven transcriptional nodes was measured in Jurkat cell lines containing a luciferase reporter under the control of NFAT, NF-kB, or AP-1. To assess anti-tumor activity of the inhibitor in vitro, a three-dimensional GFP-expressing human breast tumor spheroid coculture assay with CD8+ T cells was established. Tumor lysis was determined by assessing the reduction of GFP signal and supernatants were collected to measure IFN-γ and granzyme B production. In parallel, to further confirm the activation of T cells by the inhibitor, splenocytes from OT-I mice were stimulated and supernatants were collected for IL-2 quantification. Furthermore, Gilead’s inhibitor was evaluated in multiple mouse tumor models to assess anti-tumor efficacy as monotherapy and in combination with checkpoint antibodies.

Results Gilead’s DGKα inhibitor enhanced DAG-mediated TCR signaling pathways (AP-1 and NF-kB), leading to augmented T cell activation, as measured by increased IL-2, IFN-γ and granzyme B secretion, that resulted in increased T cell-dependent killing of tumor cells in vitro. In colorectal (CT26 and MC38) and melanoma (B16F10) mouse tumor models, the inhibitor demonstrated tumor growth inhibition as a monotherapy and improved the efficacy of α-PD-1 and α-CTLA-4.

Conclusions Specific inhibition of DGKα by Gilead’s inhibitor enhances effector T cell function, leading to robust tumor growth inhibition in mouse tumor models as a monotherapy and potentiating the activity of checkpoint blockade.