LACTATE MODULATION IN CANCER AND IMMUNE CELLS IS ASSOCIATED WITH ANTITUMOR EFFICACY OF DUAL MCT1/MCT4 INHIBITOR NGY-091

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Background Metabolic profiles of cells in the tumor microenvironment (TME) are known to be altered during the onset and progression of a tumor. Lactate is a key metabolic end-product of glycolysis that plays an important role in tumor progression and antitumor immunity. NGY-091, our first-in-class inhibitor of lactate transporters MCT1 and MCT4, has demonstrated a strong in vitro and in vivo antitumor efficacy.

Methods Cytotoxicity was evaluated in cancer cells by MTS assay. Lactate level was quantified to demonstrate on-target activity of NGY-091 in both cancer and immune cell types present in the TME by lactate glo assay (Promega). Human CD4+ T, CD8+ T and Treg cells were activated in the presence or absence of NGY-091, and expression of activation markers/cytokines and viability were assessed by flow cytometry. Human monocytes were differentiated to MDSCs followed by treatment with NGY-091. MDSC function and viability were examined by flow cytometry.

Results NGY-091 displayed a blockade of lactate import through MCT1 and lactate export through MCT4. The cytotoxic effect of NGY-091 was mediated by lactate import inhibition through MCT1 and the subsequent decrease in mitochondrial respiration. When studying the phenotypic effect of NGY-091 in immune cells under culture conditions mimicking the TME, we found that CD4+ and CD8+ T cells were strongly activated without affecting their proliferative ability. In contrast, viability and function of suppressive immune cells, Treg and MDSCs, were significantly reduced by NGY-091. In CD4+ and CD8+ T cells, NGY-091 treatment increased accumulation of intracellular lactate and subsequently decreased extracellular lactate that indicated blockade of glycolysis. We examined lactate import by MDSCs and Tregs, as these cells are known to utilize lactate as a source of energy, and found that NGY-091 strongly decreased lactate import in these cells.

Conclusions NGY-091 modulates lactate transport to induce direct cytotoxicity in cancer and activate robust antitumor immunity.