NOVEL PHARMACOLOGICAL APPROACH TO INDUCE DIRECT KILLING OF CANCER AND ACTIVATE ANTITUMOR IMMUNITY VIA INHIBITION OF MONOCARBOXYLATE TRANSPORTERS

Sanbad Sharma*, Nicole Bowman, Sanath Wijerathna, Maolin Yu, Jennifer Duffy, Jaime Escobedo, Nelly Kuklin, Vincent Sandanayaka. Nirogy Therapeutics, Framingham, MA, USA

Background Tumor progression and metastasis is driven by metabolic rewiring of cancer cells as well as cell types involved in the tumor microenvironment (TME). One key hallmark of tumor progression is the aberrant increase in glycolytic flux which creates a TME rich in lactate. The abundance of lactate in the TME serves as a great source of energy to immunosuppressive cell populations, such as Tregs and MDSCs, that thrive on lactate. Increase in immunosuppressive cells in tumors diminish the cytotoxic/effector function of CD8+ T cells thereby converting tumors to be immune-cold and resistant to therapies. Therefore, simultaneous blockade of lactate export by cancer cells and lactate import by suppressive immune cells is a novel therapeutic strategy to treat cancer.

Methods Cytotoxicity was evaluated in cancer cells by MTS assay. Lactate import/export was quantified using Lactate-glo assay (Promega). In vivo efficacy in CDX and PDX models was evaluated in NOD/SCID mice model. 4T1 and MC38 syngeneic tumor models were used to study synergistic effect of NGY-091 in combination with immune checkpoint blockade therapies. Activated/differentiated human CD4 T, CD8 T, MDSCs and Tregs were analyzed for markers/cytokines/viability by flow cytometry.

Results NGY-091 exhibited a potent cytotoxicity in cancer cells in vitro by modulating transport of monocarboxylates. The mode of action of NGY-091 involved the blockade of lactate import through MCT1 and MCT4-mediated lactate export. Furthermore, NGY-091 demonstrated significant direct killing of cancer cells in vivo in human CDX and PDX models. In syngeneic models of 4T1 and MC38 murine tumors, NGY-091 treatment showed synergistic tumor growth inhibition when combined with immune checkpoint inhibitors, in addition to a significant tumor growth reduction by NGY-091 treatment alone. Immune profiling of 4T1 tumors by flow cytometry indicated a robust activation of antitumor immunity. Specifically, increases in effector T cell populations, CD8/Treg ratio and tumor-suppressive M1 macrophages was evident in NGY-091 treated tumors. On the other hand, tumor supporting M2 macrophages were found to be downregulated. These observations were further validated by in vitro studies using human immune cells where NGY-091 treatment strongly increased and activated effector CD4 and CD8 T cells. Importantly, NGY-091 significantly reduced the growth and functionality of Treg and MDSCs.

Conclusions Therefore, NGY-091 intervenes with two key hallmarks of cancer – metabolism and immunity and has a strong therapeutic utility in cancer treatment.