Cancer-Specific NF-kB Inhibition via Novel Small Molecule IT-848: Investigating IT-848 Monotherapy and Combination Therapy for Hematological Malignancy Treatment

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Developing clinical Nuclear-factor-kappa-B (NF-κB) inhibitors persists as an unresolved challenge due to the duality of NF-κB. NF-κB activity in T-cells exerts a protective effect by stimulating anti-tumor immunity, yet NF-κB activity in cancer cells exerts a destructive effect by promoting immunotherapy failure and drug resistance. A novel, direct NF-κB inhibitor, 9-chloro-8-(hexyloxy)-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dione (IT-848), exhibits clinical promise yet required further analysis in combination with current cancer treatments. To test the potential of IT-848 and Chimeric Antigen Receptor (CAR)-T cell combination therapy in evading NF-κB-dependent immunotherapy failure, cytotoxic T-cell and CD19-CAR-T cell cultures were treated with IT-848. Flow cytometry of cytotoxic T-cells revealed IT-848 did not impede Interleukin-2, Interferon-gamma, nor Tumor necrosis factor-alpha cytokine production, indicating IT-848 does not impair essential anti-tumor immune function. Luciferase assay and flow cytometry of CD19-CAR-T cells revealed that IT-848 does not reduce CAR-T cell anti-EL4 lymphoma cell cytotoxicity, yet diminishes Interleukin-6 production ($p<0.01$), thereby supporting IT-848 can attenuate immunotherapy failure without compromising anti-tumor immunity. To maximize the potential of IT-848 in preventing NF-κB-dependent drug resistance, EL4 lymphoma cells were treated with IT-848, CD19-CAR-T cells, and Histone Deacetylase Inhibitors. Triple therapy demonstrated an additive effect on minimizing EL4 lymphoma cell growth ($p<0.05$), supporting advantageous applications of IT-848 in combination therapies. IT-848 is a potent, clinically relevant monotherapy and combination therapy that also minimizes adverse side effects during hematological malignancy treatment.

Awards Won:

Third Award of $1,000