DISCOVERY OF POTENT CBL-B INHIBITORS DEMONSTRATING ENHANCED IMMUNE CELL ACTIVITY AND TUMOR GROWTH INHIBITION IN MURINE SYNGENIC MODELS

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Background Casitas B-lineage lymphoma b (Cbl-b), a RING finger E3 ligase and a member of a highly conserved family of Cbl proteins, catalyzes the ubiquitination of substrate proteins to regulate multiple signaling events in a variety of cell types, including immune cells. In T cells, Cbl-b negatively regulates adaptive immune system signaling by establishing the threshold for the activation of antigen receptors. Additionally, Cbl-b regulates the function of other immune cell types, including NK cells, dendritic cells (DC) and monocytes. Cbl-b deficient T cells no longer require a costimulatory signal to be fully activated. Cbl-b KO mice spontaneously reject tumors via an enhanced immune response. Taken together, these findings point to Cbl-b inhibitors as having the potential to be highly efficacious immuno-oncology agents.

Methods A structure-based drug design approach was used to identify potent inhibitors of Cbl-b. Biochemical and biophysical assays, in vitro cellular assays, as well as primary human and mouse immune cell assays assay were used to profile inhibitor compounds. In vivo activity of Cbl-b inhibitors was evaluated using an anti-CD3 mouse model and a CT-26 syngeneic mouse model.

Results Cbl-b inhibitors potently bind to Cbl-b, preventing Cbl-b phosphorylation and binding to E2. In cells, compound treatment results in enhanced transcriptional activity and robust cytokine secretion from primary human and mouse T cells. In vivo, an increase in cytokines and T cell activation markers was observed after a single dose of compound. Repeated dosing of compound showed dose-dependent anti-tumor activity in the colorectal CT-26 syngeneic model.

Conclusions Potent Cbl-b inhibitors demonstrate strong T cell activation and anti-tumor activity in a syngeneic tumor model. These data support Cbl-b inhibitors as a promising therapeutic opportunity for cancer treatment.