Arginase Inhibitor CB-1158 Elicits Immune-Mediated Anti-Tumor Responses as a Single Agent and Enhances the Efficacy of other Immunotherapies


Calithera Biosciences Inc., South San Francisco, California, USA

Abstract

Myeloid-derived suppressor cells (MDSCs) and polymorphonuclear cells (PMNs) limit effective anti-tumor immune responses. However, there are no approved clinical agents that directly antagonize the activity of these cell types. Some of the limitations of active immunotherapies are the high level of tumor immune cell exhaustion and the lack of effective immune cell infiltration. CB-1158 is a highly potent small molecule inhibitor of arginase-1, a nutrient sensor that regulates immune cell homeostasis and function. CB-1158 has high selectivity for arginase-1 in vitro and preclinical studies show that it is not cytotoxic to cancer cell lines or primary T-cells. CB-1158 elevates arginine in tumors and exhibits single agent anti-tumor efficacy in several mouse syngeneic tumor models. CB-1158 increases levels of tumor Th1 T-cells and reduces levels of tumor macrophages. CB-1158 also enhances the efficacy of adoptive T-cell therapy and other immunotherapies.

CB-1158 Elevates Arginine in Tumors

CB-1158 Potently Inhibits Arginase

CB-1158 has Single-Agent Anti-Tumor Efficacy

CB-1158 Increases Inflammation in the Tumor

CB-1158 Synergizes with Adoptive T-Cell Therapy

CB-1158 Elevates Plasma Arginine in Patients

CB-1158 block arginase activity, maintained arginine levels, and allowed T-cells to proliferate in the presence of peptide+pulsed DCs. CB-1158 also reversed myeloid cell-mediated T-cell suppression in vitro and in vivo. CB-1158 expanded CD8 T-cells and decreased M2 macrophages in several mouse syngeneic tumor models. Treatment with CB-1158 also enhanced the efficacy of adoptive T-cell therapy and other immunotherapies.

CB-1158 Increases CD8 T-cells and Decreases M2 macrophages

CB-1158 Synergizes with Adoptive T-Cell Therapy

CB-1158 Elevates Plasma Arginine in Patients

CB-1158 increases tumor arginine levels and has single agent efficacy in multiple syngeneic mouse models. CB-1158 elevates tumor Th1 T-cell levels and reduces tumor macrophage levels. CB-1158 also enhances the efficacy of adoptive T-cell therapy and other immunotherapies.