Arginase inhibitor CB-1158 is a novel immuno-oncology agent that targets tumor-infiltrating suppressive myeloid cells


Abstract

Depletion of arginase by arginase-expressing myeloid cells contributes to an immunosuppressive tumor microenvironment that inhibits proliferation of effector lymphocytes. Pharmacological inhibition of arginase produced by myeloid cells such as neutrophils, macrophages, and myeloid-derived suppressor cells (MDSC) is expected to restore arginase levels and allow T-cells to proliferate, thereby leading to an immunomediated anti-tumor response. CB-1158 is a potent inhibitor of arginase (IC₅₀ = 100 nM). In a co-culture system with human neutrophils and T-cells, CB-1158 blocked arginase activity, increased arginase levels in the media, and restored proliferation of T-cells (IC₅₀ = 160 nM). In immunocompetent mice bearing Lewis Lung Carcinoma (LLC) syngeneic tumors, BID oral dosing of 100 mg/kg CB-1158 showed good exposure in plasma and tumor, led to pharmacodynamic increases in arginase levels in plasma (3-fold) and tumor (4-fold), resulting in tumor growth inhibition of 54% and was well tolerated. CB-1158 treatment increased pro-inflammatory cytokine and chemokine levels in LLC tumors and had no anti-tumor activity in immunocompromised SCID mice, consistent with an immunemediated mechanism of action. Given these findings, we investigated whether CB-1158 would combine with checkpoint inhibitors a-CTLA-4 or a-PD-1. CB-1158 in combination with a-CTLA-4, increased the levels of tumor-infiltrating CD8 T-cells in LLC-tumor bearing mice. In combination with a-CTLA-4 and a-PD-1, CB-1158 decreased tumor growth and metastatic burden in the highly refractory 4T1 breast cancer model. These results support the development of CB-1158, a first-in-class arginase inhibitor, as a novel immuno-oncology agent that targets the immunosuppressive effects of tumor-infiltrating myeloid cells.

Arginase Depletion Blocks T-cell and NK-cell Activation

Figure 1: Proliferation of anti-CD3/anti-CD28-stimulated human T-cells measured by flow cytometry with anti-CD4 and anti-CD8 staining after a 4 day incubation in media containing varying concentrations of arginase

Arginase 1 Expression in Cancer Patients

Figure 2: (A) Immunohistochemistry staining for arginase 1 in sections of normal human tissues (N = 33 tissues analyzed) and human tumor tissues (N = 13 tumor histologies analyzed). Representative images are shown (red arrow point to arginase-expressing myeloid cells). (B) Quantitation by digital histophotometry of arginase 1-expressing myeloid cells in human tumor tissues. (C) ELISA determination of arginase 1 levels in plasma samples from cancer patients.

CB-1158 Elevates Arginase in Tumors

Figure 3: (A) Schematic of arginase reaction. (B) Enzyme values for inhibition of arginase reaction by CB-1158 using various sources of arginase as indicated. Activity was measured by xan and ornithine production using a dose titration of CB-1158.

CB-1158 Increases Inflammation in LLC Tumors

Figure 4: (A) Concentration of CB-1158 in (A) plasma or (B) Lewis Lung Carcinoma (LLC) tumor lysates from C57B1/6 mice dosed orally 5 doses of CB-1158 on an 8 day schedule. Samples were collected 2 days after the last dose of CB-1158 (N = 5 per group). (C) Arginase concentration in (C) plasma or (D) tumor of samples in A-B.

CB-1158 Inhibits Human Arginase and Reverses Immunossuppression of T-cells

Figure 5: (A) Plasma CB-1158 effect on T-cell recovery and arginase inhibition. (B) Plasma CB-1158 effect on T-cell recovery and arginase inhibition. (C) Plasma CB-1158 effect on T-cell recovery and arginase inhibition. (D) Tumor Arginase effect on T-cell recovery and arginase inhibition.

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Figure 6: (A) Lewis Lung Carcinoma cells were implanted in C57Bl/6 mice and mice were dosed orally with vehicle or CB-1158 twice daily at 100 mg/kg. (B) An additional group of mice in (A) were treated with anti-CD3 prior to the start of CB-1158 dosing. (C) In a separate experiment, tumor-bearing mice were treated with vehicle or CB-1158 in the presence or absence of anti-CD2 at 100 mg/kg each (n = 5 per group). *P < 0.001, **P < 0.01, ns, not significant.

Conclusions

- CB-1158 potently inhibits arginase and reverses MDSC/neutrophil induced suppression of T-cell proliferation
- CB-1158 increases tumor and plasma arginase levels and has single agent efficacy in syngeneic mouse models
- CB-1158 efficacy is immune mediated and creates a pro-immunogenic tumor microenvironment
- In the refractory 4T1 model, addition of CB-1158 to anti-PD-1 and anti-CTLA-4 results in tumor growth inhibition
- CB-1158 is currently in IND-enabling studies