Targeting Tumor Glutamine Metabolism with CB-839 Enhances the Efficacy of Immune Checkpoint Inhibitors

Andrew MacKinnon, Jason Chen, Matt Gross, Gisele Marqueter, Peter Shwonet, Natalia Sotirova, Susanne Steggerda, Francesco Parlati

Calithera Biosciences Inc., South San Francisco, CA

Abstract

Background

Tumor cell proliferation and a Warburg metabolism are intrinsically linked, providing a metabolic source for tumor cell growth. Prevention of T-cell activation and cell division presenting a novel approach to enhance the efficacy of immune checkpoint inhibitors. Theoretically, T-cell activation in the absence of glutamine inhibited cell proliferation and the expression of cell surface activation markers. BTLA, suggesting that T-cell activation in the absence of glutamine may be sufficient to induce an exhausted phenotype.

Introduction

Glutamine is a critical amino acid for T-cell proliferation and metabolic reprogramming in activated T-cells. CB-839 had only minimal impact on T-cell proliferation, highlighting differences in glutamine utilization pathways between T-cells and tumor cells.

Tumor Cells and T-Cells Require Glutamine for Proliferation and Survival

A. Tumor cells are depleted for glutamine for proliferation and survival

B. T-cell division is dependent on glutamine

CB-839 is a Glutaminase Inhibitor with Broad Anti-tumor Activity

A. CB-839 treatment reduces intracellular glutamate or glutamine-derived metabolites

B. CB-839 has and proliferation activity across a broad panel of cancer cells

CB-839 Blocks Tumor Cell Glutamine Consumption and Restores T-Cell Division in Vivo

A. How tumor cell glutamine consumption is reduced due to glutaminase inhibition

B. Glutamine deprivation downregulates Myc and blocks metabolic reprogramming in activated T-cells

CB-839 Has Minimal Impact on T-Cell Activation and Division

A. Glutamine deprivation blocks T-cell activation, proliferation, and metabolic reprogramming and prevents expression of suppressive markers

B. Glutamine deprivation blocks T-cell activation and metabolic reprogramming

C. Glutamine deprivation blocks T-cell proliferation

D. Hypothesis for glutamine in the tumor microenvironment can suppress T-cell proliferation

CB-839 Increases Glutamine in Tumors in Vivo

A. Glutamine deprivation is reversed by glutamine depletion

B. Glutamine deprivation is reversed by glutamine depletion

C. Glutamine deprivation is reversed by glutamine depletion

D. Glutamine deprivation is reversed by glutamine depletion

CB-839 Synergizes With Immune Checkpoint Inhibitor

A. Tumor suppression with combination of immune checkpoint inhibitor and CB-839

B. Tumor suppression with combination of immune checkpoint inhibitor and CB-839

C. Tumor suppression with combination of immune checkpoint inhibitor and CB-839

D. Tumor suppression with combination of immune checkpoint inhibitor and CB-839

Potential Biomarkers For Tumors With Glutamine Deprived T-cells

A. Metabolic reprogramming in T-cells

B. Metabolic reprogramming in T-cells

C. Metabolic reprogramming in T-cells

D. Metabolic reprogramming in T-cells

Conclusions

A. Glutamine is a novel therapeutic target for cancer by selectively targeting tumor metabolism as a means of enhancing tumor cell proliferation and survival

B. Glutamine deprivation blocks T-cell activation, proliferation, and metabolic reprogramming and prevents expression of suppressive markers

C. CB-839 has limited impact on T-cell proliferation

D. Glutamine deprivation blocks T-cell proliferation

E. Glutamine deprivation blocks T-cell proliferation

F. Glutamine deprivation blocks T-cell proliferation

G. Glutamine deprivation blocks T-cell proliferation

H. Glutamine deprivation blocks T-cell proliferation

I. Glutamine deprivation blocks T-cell proliferation

J. Glutamine deprivation blocks T-cell proliferation

K. Glutamine deprivation blocks T-cell proliferation

L. Glutamine deprivation blocks T-cell proliferation

M. Glutamine deprivation blocks T-cell proliferation

N. Glutamine deprivation blocks T-cell proliferation

O. Glutamine deprivation blocks T-cell proliferation

P. Glutamine deprivation blocks T-cell proliferation

Q. Glutamine deprivation blocks T-cell proliferation

R. Glutamine deprivation blocks T-cell proliferation

S. Glutamine deprivation blocks T-cell proliferation

T. Glutamine deprivation blocks T-cell proliferation

U. Glutamine deprivation blocks T-cell proliferation

V. Glutamine deprivation blocks T-cell proliferation

W. Glutamine deprivation blocks T-cell proliferation

X. Glutamine deprivation blocks T-cell proliferation

Y. Glutamine deprivation blocks T-cell proliferation

Z. Glutamine deprivation blocks T-cell proliferation