eFT508, a Potent and Selective Mitogen-Activated Protein Kinase Interacting Kinase (MNK) 1 and 2 Inhibitor, is Efficacious in Preclinical Models of Diffuse Large B-Cell Lymphoma (DLBCL)

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Abstract

Dysregulated translation of messenger RNA (mRNA) plays a role in the pathogenesis of multiple solid tumors and hematological malignancies. MNK1 and MNK2 integrate signals from several oncogenic and immune signaling pathways, including RAS, p38, and Toll-like receptor (TLR) pathways, by phosphorylating several key downstream translation regulators, including eIF4E, eIF4A, eIF4G, and PABP, and other key effector proteins including hnRNPA1 and PUMA. Through phosphorylation of these regulatory proteins, MNK1 and MNK2 selectively regulates the translation of subsets of proteins important for tumorigenesis

1. Introduction

MNK1 and MNK2 are serine/threonine kinases that integrate signals from several oncopgenic and immune signaling pathways such as, RAS, p38 and TLR signaling pathways.

The phosphorylation of key MNK substrates, such as eIF4E and hnRNPA1, selectively modulate oncogenic protein expression through the regulation of translation initiation and mRNA stability.

eFFECTOR Therapeutics has discovered eFT508, a potent, small molecule inhibitor of MNK1 and MNK2 activity

2. Results

2.1. eFT508 Inhibits Key MNK1/2-Dependent Signaling Pathways in Cells

a. TNBC cells were treated with the indicated concentrations of eFT508 for 24 h. Cell lysates were subjected to Western Blot analysis and bands were quantitated by densitometry. The results were normalized to β-actin. All experiments were performed in triplicate and representative blots are shown.

b. TMD8 cells were treated with 10 µM eFT508 for 24 h. Aminoacyl-tRNA synthetase and hmr were harvested from the cells at various time points. The quantity of MRNA was performed by Sulfadiazine assay and calculated percent half-life were shown.

2.2. eFT508 Regulates eIF4E Activity and mRNA Half-Life

a. U2OS cells were treated with eFT508 at 10 µM and 100 µM for 24 h. The percentage of P-eIF4E inhibition was plotted as a function of the corresponding eFT508 concentration.

b. The mRNA half-life is reduced in eFT508 treated cells as compared to DMSO control. These findings are consistent with MNK1 and MNK2 inhibitor.

2.3. eFT508 Inhibits the Expression of Pro-Inflammatory Cytokines Important for Tumorigenesis

a. MDA-MB-231 cells were treated with the indicated concentrations of eFT508 for 24 h. Cell supernatants were collected and the indicated cytokines were quantitated by ELISA.

b. TMD8 cells were treated with eFT508 and everolimus. Cell lysates were immunoblotted with the indicated antibodies. The results were normalized to β-actin. All experiments were performed in triplicate and representative blots are shown.

2.4. eFT508 Inhibits the Growth of Tumor Cells in Preclinical Models of Diffuse Large B-Cell Lymphoma

a. Mice were randomized into groups of three per vehicle control or single agent treatment. The vehicle control received 100 µl of 5% Cremophor EL - 0.9% saline, 4 times a week for 4 weeks. The vehicle control group treated with eFT508 or everolimus for 14 days. The tumor volume was measured and plotted as a function of time.

b. In vivo single agent and combined activity of eFT508 with everolimus in TMD8 xenografts. The tumor volume and weight were measured and plotted as a function of time.

3. Conclusions

eFT508 is a potent, highly selective, orally bioavailable inhibitor of MNK1 and MNK2 kinases

- eFT508 blocks the production of pro-inflammatory cytokines involved in oncogenic processes

- eFT508 is well-tolerated and shows efficacy against MyD88-mutant DLBCL models in vivo

- eFT508combines effectively with targeted agents and standard of care agents (e.g. R-CHOP) in vivo

- Clinical trials in patients with hematological and other malignancies are planned

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