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)

Kevin R Webster1, Vikas K Goel1, Ivy N Hung1, Gregory S Parker1, Jocelyn Staunton1, Melissa Neal1, Jolene Molter1, Gary G Chiang1, Katti A Jessen1,2, Christopher J Wegerski1, Samuel Sperry1, Vera Huang1, Joan Chen1, Peggy A Thompson1, James R Almpanis1,3, Justin T. Ernst1, Stephen E Webber1,4, Paul A Sprengeler1 and Siegfried H Reich1

1eFFECTOR Therapeutics, San Diego; 2Present address: Pfizer, San Diego, CA; 3Annai Systems, Carlbad, CA; 4Polaris Pharmaceuticals, San Diego, CA

Introduction

Dysregulated translation of messenger RNA (mRNA) plays a role in the pathogenesis of multiple solid tumors and hematological malignancies. MNK1 and MNK2 integrally regulate translation through phosphorylation and regulated translation initiation and mRNA stability. 

- MNK1 and MNK2 are serine/threonine kinases that integrate signals from several oncogenic and immune signaling pathways, including RAS, p38, and Toll-like receptor (TLR) 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, highly selective, and orally bioavailable MNK1 and MNK2 inhibitor. eFT508 is a potent, highly selective inhibitor of MNK1 and MNK2.

Results

- eFT508 is a potent and highly selective inhibitor of MNK1 and MNK2. The IC50 of eFT508 was observed against MNK1 and MNK2 by in vitro kinase assays. eFT508 was also profiled at 1 µM against 514 kinase targets including the hydrogen SelectScreen kinase protein panel. The IC50 of eFT508 was determined against the hit with >50% inhibition from this screen. eFT508 and other potent inhibitors were selected for follow-up due to the synergy between MNK1/MNK2. In a panel of ~50 hematological cancers, eFT508 showed anti-proliferative activity and was associated with dose-dependent decreases in production of pro-tumor cell survival, migration and invasion, angiogenesis, and immune evasion, while also decreasing translation efficiency.

- eFT508 treatment relative to DMSO resulted in 4-fold decreases in TNFα and IL-6, IL-10 and CXCL10. Further evaluation of eFT508 in tumor cell lines demonstrated decreases in protein expression of CD79, MYD88, and IL-6, IL-10 and CXCL10.

- In vivo, eFT508 treatment relative to DMSO decreased the growth of select tumor models. A) Tumor growth inhibition of MYD88-mutant DLBCL xenografts was measured by immunoblot and % inhibition was plotted as a function of the corresponding eFT508 exposure-response. B) Combination Index (CI) values were determined at ED25-ED90 levels from cell proliferation measurements. CI values were determined at ED25-ED90 levels from cell proliferation measurements. C) eFT508 treatment relative to DMSO decreased the growth of select tumor models.

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.
- eFT508 combines 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.