eFT508, A Potent and Highly Selective Inhibitor of MNK 1/2, Regulates Immune Checkpoint and Cytokine Expression Promoting Anti-tumor Immunity

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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, two members of several oncogenic and immune signaling pathways (including Ras, Toll-like receptors and T-cell receptors) and crucial proteins in the regulation of cell proliferation, translation and translation initiation of and via key effector proteins including HIV-1 and PI3K. Phosphorylation of these RNA-binding proteins by MNK1 and MNK2 selectively regulates the translation and transcription of a subset of cellular mRNA transcripts that control tumor/stromal cell signaling, the tumor microenvironment and immune cell function. eFT508 is a potent and highly selective inhibitor of both MNK1 and MNK2. RNAseq profiling has demonstrated that inhibition of MNK1 and MNK2 by eFT508 selectively regulates the transcriptional and translational efficiency and mRNA stability of a subset of genes that include inflammatory cytokines/soluble molecules, regulation of stress-response, and effectors of anti-tumor immune response. Given the importance of MNK signaling and translational control to immune cell activation and deactivation, the immunomodulatory effect of eFT508 was further evaluated in both normal human immune cells in vitro and immune COMPETITIVE AND IMMUNE SIGNALING MODELS in vivo. eFT508 treatment of normal donor T cells has no deleterious effect on cDNA or control-stimulated IL-2 production, T cell proliferation or T cell survival; however, eFT508 selectively down-regulates the expression of genes related to the IL-10 and specific immune checkpoint receptors, including PD-L1 and PD-L2. Further evaluation of the mechanism of translational regulation has shown LAG3 mRNA contains specific sequence elements in the 5' untranslated region (UTR) that confer sensitivity to eFT508. In addition, the LAG3 mRNA is up-regulated upon treatment with eFT508 leading to significant inhibition of IL-10 production in activated T cells. Furthermore, eFT508 treatment results in up-regulation of MNK1, MAPK signaling and dendritic cells through an IL-10-MAPK/-JNK/MAPK/-JNK/MAPK signaling pathway. The in vivo antitumor effect of eFT508 was assessed in the CT26/BALB/c syngeneic tumor model. CT26 mouse T cell proliferation and survival were measured upon treatment with eFT508 in vitro, in vivo, daily oral treatment with 1 mg/kg of eFT508 results in significant anti-tumor activity, modulation of tumor infiltrating lymphocytes and establishment of immune memory in addition, external control of both eFT508 with either anti-PD-1 or anti-PD-L1 monomeric antibodies results in marked effects, significantly increasing the percentage of responder animals. eFT508 is currently under evaluation in two phase I clinical trials for patients with advanced solid tumors and patients with advanced lymphoma respectively. These findings support further clinical evaluation of eFT508 in combination with checkpoint inhibitors.

Results

Conclusion

- eFT508 selectively inhibits immune checkpoint receptors (PD-1, LAG3) and cytokine (IL-6) expression in vitro
- MNK1/2 control mRNA fate through specific 5' and 3' UTR elements
- eFT508 increases MHCI class II expression on the surface of antigen-presenting cells and affects DC trafficking in vivo
- eFT508 enhances central memory pool formation and cytokine secretion in T cells
- eFT508 modulates anti-tumor immunity and effectively synergizes with immune checkpoint blockade in vivo
- eFT508 is currently being evaluated in a phase 1/2 clinical trial in patients with solid tumors (NCT03265083) and in a phase 1/2 clinical trial in lymphoma (NCT03297765)