eFT508, A Potent and Highly Selective Inhibitor of MNK1 and MNK2, is an Activator of Anti-Tumor Immune Response

Kevin R Webster1, Rajesh Sharma1, Vikas K Goel1, Craig R. Stump3, Jocelyn Staunton1, Peggy A Thompson1, Gary G Chiang4, Yichen Xu4, Hyun Yong Jin5, and Davide Ruggero6
1eFFECTOR Therapeutics, San Diego, CA; 2Departments of Urology, Cellular and Molecular Pharmacology, and the Hellen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Abstract

Background: eFT508 is a potent and highly selective inhibitor of MNK1 and MNK2 kinases that function to modulate tumor immunity evasion downstream of MEK and MAPK signaling. eFT508 treatment establishes a regulatory program that promotes multiple steps in the cancer immunity cycle including antigen presentation and T cell priming, expansion of memory T cells, and prevention of T cell exhaustion. Methods: The immunological effects of eFT508 have been evaluated in the context of normal human immune cells in vitro and in immunocompetent syngeneic and genetically engineered mouse models in vivo. Results: eFT508 treatment of normal donor T cells has no deleterious effect on CD3/CD28 stimulated T cell proliferation or T cell viability in contrast to inhibitors acting upstream of MAPK signaling. eFT508 selectively downregulates key immune checkpoint proteins and the production of a subset of pro-inflammatory and immunosuppressive cytokines. In vitro mechanism of action studies have demonstrated that MNK selectively regulates gene expression at the level of mRNA translation via specific sequence elements in the 5′- and 3′-untranslated regions. In addition, eFT508 activates antigen presenting cells leading to more effective T cell priming. eFT508 also affects T cell memory formation, both in the context of specific antigen stimulation and in a mixed lymphocyte reaction, shifting the distribution of T cells towards a CD25+CD44+ central memory T cell population. eFT508 also enhances the cytotoxic function of T cells from OT-I mice stimulated with SIFNEFL peptide demonstrating a dose-dependent increase of cell killing. Consistent with the mechanisms elaborated upon in vitro, eFT508 shows significant anti-tumor activity mediated through tumor infiltrating lymphocytes in the CT26 syngeneic tumor model as well as genetically engineered mouse models of NSCLC and HCC. Conclusions: eFT508 treatment establishes a regulatory program that promotes anti-tumor immunity. eFT508 is currently under evaluation as a single agent in two phase I/II clinical trials for patients with advanced solid tumors and patients with advanced lymphoma. A biomarker driven proof of concept study, including mandatory pre- and on-treatment biopsies, to evaluate the immunological mechanism of action of the drug is planned to be initiated later this year. In addition, a phase 2 study evaluating eFT508, alone or in combination with avelumab, a PD-L1 immune checkpoint inhibitor, in microsatellite stable relapsed or refractory CRC patients is planned.

Results

- **eFT508** is a potent and highly selective inhibitor of MNK1 and MNK2 kinases. (a) Chemical structure of eFT508. (b) The IC50 of eFT508 was determined against MNK1 and MNK2 in vitro (1×10^6 cells/mL). eFT508 was also profiled at 1×10^4 U/mL using the in vitro platelet release assay. (c) MNK1 and MNK2 are S/T protein kinases that integrate signals from upstream protein kinases. (d) The translation of key regulators of the cancer immunity cycle including antigen presentation and T cell priming, expansion of memory T cells, and prevention of T cell exhaustion. (e) The immunological effects of eFT508 have been evaluated in the context of normal human immune cells in vitro and in immunocompetent syngeneic and genetically engineered mouse models in vivo. Results: eFT508 treatment of normal donor T cells has no deleterious effect on CD3/CD28 stimulated T cell proliferation or T cell viability in contrast to inhibitors acting upstream of MAPK signaling. eFT508 selectively downregulates key immune checkpoint proteins and the production of a subset of pro-inflammatory and immunosuppressive cytokines. In vitro mechanism of action studies have demonstrated that MNK selectively regulates gene expression at the level of mRNA translation via specific sequence elements in the 5′- and 3′-untranslated regions.

- **MNK1 and MNK2 are S/T protein kinases that integrate signals from upstream protein kinases.**

- **The translation of key regulators of the cancer immunity cycle including antigen presentation and T cell priming, expansion of memory T cells, and prevention of T cell exhaustion.**

- **Results:**

- **eFT508 increases dendritic cell maturation and trafficking in vivo.**

- **eFT508 enhances the formation of the T cell central memory pool.**

- **eFT508 shows significant anti-tumor activity mediated through tumor infiltrating lymphocytes in the CT26 syngeneic tumor model.**

- **Current evaluation as a single agent in two phase I/II clinical trials for patients with advanced solid tumors and patients with advanced lymphoma.**

- **A biomarker driven proof of concept study, including mandatory pre- and on-treatment biopsies, to evaluate the immunological mechanism of action of the drug is planned to be initiated later this year.**

Conclusions:

- **eFT508 selectively inhibits immune checkpoint receptors (PD-1, LAG-3) and cytokine (IL-10) expression.**

- **MNK1/2 control mRNA transcription via 5′ and 3′ UTR elements.**

- **eFT508 increases MHC class II expression on the surface of antigen-presenting cells and enhances the efficacy of PD-1 and PD-L1 immune checkpoint blockade.**

- **eFT508 can block induced T regulatory cell differentiation and enhance central memory pool formation and cytotoxic function in T effector cells.**

- **eFT508 modulates anti-tumor immunity and effectively synergizes with immune checkpoint blockade in vivo.**

- **eFT508 is currently being evaluated in phase I clinical trials as a single agent in patients with solid tumors (NCT02665083) and lymphoma (NCT03259765), and as a single agent in combination with avelumab in MSS colorectal cancer (NCT03258398).**