eFT508, A Potent and Highly Selective Inhibitor of MNK 1/2, Regulates T Cell Differentiation

Promoting an Anti-tumor Immune Response

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Abstract

An effective and durable T cell response is a cornerstone of current immunotherapies. We show that eFT508, a potent, selective inhibitor of MNK1 and MNK2, establishes a program that promotes multiple steps in the cancer immune cycle including expansion of memory T cells and prevention of T cell exhaustion. Using OT-1 and OT-2 T cell transgenic systems, we show that eFT508 shifts the distribution of T cells towards a CD8+CD44+CD62L− central memory (CM) phenotype in both CD4+ and CD8+ T cells upon activation with SIINFEKL peptide in vitro without adverse effects on T cell proliferation, interference of production of cytokine function. Similar effects are seen in vivo, where eFT508 treatment also enriches the CM T cell pool in a SIINFEKL vaccine-induced OT-1 adoptive T cell transfer model, which results in increased persistence as demonstrated by a higher memory-recall T cell response upon re-challenge. In addition, the CM bias elicited by eFT508 remains dominant when combined and compared with other TCR agonists, such as 4-1BB, OX40 and GITR, or checkpoint inhibitors, such as PD-L1, PD-L1 and CTLA4, suggesting that eFT508 can affect the rate of T cell differentiation in these combinations. eFT508 treatment also reduces the expression of education markers such as PD-L1, LAG3 and TIM3 leading to increased cytotoxic T cell function. eFT508 is currently under evaluation as a single agent in two phase I/II clinical trials for patients with solid tumors and patients with advanced lymphomas. In addition, a phase II study evaluating eFT508, alone or in combination with axolimumab, a PD-L1 immune checkpoint inhibitor, in micrascopic stable relapsed or refractory CRC patients is ongoing. The pre-clinical studies presented here provide further evidence that eFT508 may combine well with additional immunotherapies beyond checkpoint blockade.

Introduction

T cell responses are a key component of successful antitumor immune responses. To date, most immunotherapies, including immune checkpoint inhibitors and engineered T cells, have failed to generate durable and effective antitumor T cell responses. It is now clear that, in addition to the naive T cell population, memory T cell subsets are key components for antitumor immune responses in the context of vaccines and immunotherapies. T cell memory can be defined as an increase in the percentage of cells that are CD45RA−CD62L− and a decrease in the percentage of CD45RA−CD62Lhi cells in memory T cells.

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Results

Figure 1. eFT508 selectively downregulates expression of key immuno-suppressive factors in activated T cells. Primary human T cells were stimulated with SIINFEKL peptides in the presence of the indicated concentrations of compound. A) Whole cell lysates from 4 × 10^6 T cells isolated from 5 healthy donors were stimulated for 24 h with SIINFEKL peptides in the presence of eFT508 and analyzed for CD86, PD-L1, TIM3, LAG3, and cell viability by flow cytometry (p positive cells) or p-nitroanilide (pNA) by ELISA. Data points are plotted as % inhibition of each marker relative to the vehicle-activated (VehAct) control cell.

Figure 2. eFT508 drives T cell activation and proliferation in the NKR setting. Peritoneal macrophages, isolated from BALB/c mice, were incubated with the indicated concentrations of eFT508 for 24 h, washed and then mixed with purified OT-I T cells. a) The cells were stimulated with SIINFEKL and a CD40 agonist for an additional 4 days. Cells were analyzed for CD8 and CellTrace Violet by flow cytometry. 

Figure 3. eFT508 induces key dendritic cell activation markers and trafficking in vivo. A) OT-I T cells were adoptively transferred into B6.SJL mice that had been immunized with 50 µg/ml SIINFEKL peptide, either with or without eFT508 (1 mg/kg). For CD8+ lymphocyte analysis, the percentage and absolute number of CD8+ T cells were determined from the indicated conditions of eFT508 in a SIINFEKL vaccine-induced OT-1 adoptive T cell transfer model, which results in increased persistence as demonstrated by a higher memory-recall T cell response upon re-challenge. In addition, the CM bias elicited by eFT508 remains dominant when combined and compared with other TCR agonists, such as 4-1BB, OX40 and GITR, or checkpoint inhibitors, such as PD-L1, PD-L1 and CTLA4, suggesting that eFT508 can affect the rate of T cell differentiation in these combinations. eFT508 treatment also reduces the expression of education markers such as PD-L1, LAG3 and TIM3 leading to increased cytotoxic T cell function. eFT508 is currently under evaluation as a single agent in two phase I/II clinical trials for patients with solid tumors and patients with advanced lymphomas. In addition, a phase II study evaluating eFT508, alone or in combination with axolimumab, a PD-L1 immune checkpoint inhibitor, in micrascopic stable relapsed or refractory CRC patients is ongoing. The pre-clinical studies presented here provide further evidence that eFT508 may combine well with additional immunotherapies beyond checkpoint blockade.

Conclusions

- eFT508 promotes antigen presentation and formation of the T cell pool while enhancing cytotoxic T cell function
- eFT508 promotes central memory balance in combination with co-stimulatory agonists or checkpoint antagonists
- eFT508 modulates anti-tumor immunity and effectively synergizes with immune checkpoint blockade in vivo
- eFT508 is currently being evaluated in phase 1/2 clinical trials as a single agent in patients with solid tumors (NCT03260908) and as a single agent in combination with avelumab in MSS colorectal cancer (NCT03258398).