Development of FPA157, an anti-CCR8 depleting antibody engineered to preferentially eliminate tumor-infiltrating T regulatory cells

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Abstract

Background: The clinical success of PD-1- and CTLA-4-directed immune checkpoint inhibitors highlights the key contribution of immunosuppression to limiting effective antitumor responses. However, as many patients do not respond to anti-PD-1 or CTLA-4 therapy [1-3], novel therapeutics that target additional immune-suppressive mechanisms are needed. Regulatory T cells (Tregs) inhibit immune responses in the tumor microenvironment via multiple suppressive mechanisms [4,5]. Existing Treg-targeting agents lack specificity for intratumoral Tregs and can also deplete effector cells, a property that has likely contributed to the lack of clinical activity observed to date for these agents. CCR8 (C, chemokine receptor 8) is selectively expressed on highly activated intratumoral Tregs, its high expression correlates with poor prognosis in multiple human tumor types [6,7] and depletion of CCR8– Tregs in preclinical models elicited potent antitumor activity. These observations provided rationale for the development of a CCR8-specific human depleting antibody.

Methods: Human FPD37 and CCR8 expression was correlated across multiple tumor types using TSGA datasets and expression of CCR8 evaluated in primary tumor explants and PDX mice by flow cytometry. The efficacy of anti-CCR8 antibody treatment was evaluated in the MC38 and CT26 murine tumor models. The depletion of Tregs following anti-CCR8 treatment was assessed by flow cytometry. Flow cytometric-based binding assays were performed using cell lines stably expressing human or cynomolgus CCR8. Purified human NK cells were co-cultured with CCR8– target cells and flow cytometry used to evaluate antibody-dependent killing activity.

Results: CCR8 expression was highly correlated with FoxP3 across multiple cancer subtypes and was low to absent on effector T cells. Importantly, CCR8 was not detected on any peripheral human leukocyte subset. In murine tumor models, anti-CCR8 antibody treatment reduced tumor growth in a dose- and Fcg-dependent manner and reached in complete regressions and the development of memory. Tumor shrinkage was associated with a reduction in intratumoral Tregs and increased representation of intratumoral CD8 T cells. FPA157 is a highly specific human and cynomolgus CCR8 antibody that does not bind closely related chemokine receptors. FPA157 was engineered to enhance antibody-dependent cell cytotoxicity (ADCC) and elicited potent NK-mediated killing of target cells expressing CCR8 at levels observed on human intratumoral Tregs.

Conclusions: FPA157 is a CCR8-specific monoclonal antibody with ADCC activity that FreePrime is developing for the treatment of cancer. Depletion of CCR8– Tregs induced substantial antitumor activity in pre-clinical models, thus supporting the clinical evaluation of FPA157 as a novel approach to alleviate immune suppression in the microenvironment of human solid tumors.

FPA157: Mechanism of Action

Figure 1: CCR8 is Preferentially Expressed by Foxp3+ T cells Within Tumors

Figure 2: CCR8 Expression Is Restricted to Intratumoral Tregs

Figure 3: Anti-mCCR8 Antibody Demonstrates Single-Agent Anti-Tumor Efficacy in Multiple Tumor Models

Figure 4: FPA157 is a Cynomolgus Cross-reactive Anti-human CCR8 Antibody

Figure 5: Potent Killing of Target Cells Expressing CCR8 at Levels Observed on Human Intratumoral Tregs

Figure 6: FPA157 Specifically binds HXK293 cells expressing human or cynomolgus CCR8, but not to parental or murine CCR8-expressing cells. FPA157 binding was measured by flow cytometry.

Conclusions

- Expression analyses confirmed that CCR8 expression is highly restricted to intratumoral Tregs.
- In preclinical models, depletion of intratumoral CCR8+ Tregs results in significant antitumor activity, while sparing peripheral Treg subsets.
- Intratumoral CCR8+ Treg depletion elicits an anti-tumor memory response highlighting that elimination of intratumoral Treg suppression can enhance effector T cell function and memory formation.
- FPA157 is an ADCD enhanced human monoclonal antibody that elicits potent NK-dependent killing of CCR8+ target cells bearing receptor levels observed in human solid tumors.
- Dose depletion of intratumoral Tregs via CCR8-targeting may yield an improved therapeutic index when compared against agents that impact peripheral Tregs and/or effector T cell populations.

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References