Potent and selective C-C chemokine receptor (CCR4) antagonists potentiate anti-tumor immune responses by inhibiting regulatory T cells (T<sub>reg</sub>)

FLX Bio, Inc. South San Francisco, CA

Abstract

Naturally suppressive CD8<sup>+</sup> T<sub>eff</sub> T<sub>reg</sub> were essential for immune tolerance. Although T<sub>reg</sub>-induced suppression of effector cells is a major contributor to immune control, CCR4 antagonists have been shown to potentiate anti-tumor immune responses. Human T<sub>reg</sub>-induced CD8<sup>+</sup>-T<sub>eff</sub> was higher than expected CD8<sup>+</sup>-T<sub>reg</sub>-induced CD8<sup>+</sup>-T<sub>eff</sub> in the NK cells of CCR4 antagonist treatment of T<sub>reg</sub>-induced CD8<sup>+</sup>-T<sub>eff</sub>. The findings indicate that CCR4 antagonists may have potential in combination with T<sub>reg</sub>-induced CD8<sup>+</sup>-T<sub>eff</sub> for the treatment of tumors. The results suggest that CCR4 antagonists may have potential in combination with T<sub>reg</sub>-induced CD8<sup>+</sup>-T<sub>eff</sub> for the treatment of tumors.

FLX Antagonist can be Dosed to Cover the Mouse T<sub>reg</sub> Chemotaxis I<sub>sp</sub>

FLX Antagonist are Highly Potent Against Mouse and Human T<sub>reg</sub> Chemotaxis

CCR4 is a Dominant Regulator of T<sub>reg</sub> in Human Tumors

FLX CCR4 Antagonists Potentiate Various IO Agents

Conclusions

- CCR4 is the most prevalent chemokine receptor on human T<sub>reg</sub>.
- CCR4 antagonists are elevated in human tumors and their expression levels correlate with PD<sub>1</sub> T<sub>eff</sub> markers.
- FLX CCR4 antagonists potently and selectively block against activation in both a calcium flux assay and ex vivo chemotaxis assay in 100% human serum.
- FLX CCR4 antagonists selectively block T<sub>reg</sub> migration into PAM3 tumors.
- Unlike depleting antibodies (e.g., gC<sub>C</sub> T<sub>reg</sub>) in skin, blood and spleens are not reduced with FLX CCR4 antagonists.
- The addition of FLX CCR4 antagonists to clinically relevant antibodies, such as g<sub>PD<sub>1</sub></sub> or g<sub>CTLA-4</sub>, shows significantly improved tumor growth inhibition and regression rates.
- These data demonstrate that a potent and selective CCR4 antagonist may be a tumor-selective and potentized approach to inhibit T<sub>reg</sub>-mediated tumor function and support a production of anti-tumor immune response.
- A FLX CCR4 antagonist is scheduled to begin clinical trials in 2017.