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SRF114, AN AFUCOSYLATED ANTI-CCR8 ANTIBODY, DEPLETES INTRATUMORAL TREG CELLS AND REDUCES TUMOR GROWTH

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Background Intratumoral regulatory T (Treg) cells promote an immunosuppressive tumor microenvironment, and their increased frequency correlates with poor clinical prognosis.¹⁻⁴ Gene expression profiling has identified chemokine receptor 8 (CCR8) as being highly upregulated by intratumoral Treg cells compared to their lymphoid tissue and blood counterparts, as well as other immune cell types.^{5,6} Because of this restricted expression, using anti-CCR8 antibodies capable of inducing antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) to deplete intratumoral Treg cells represents an attractive therapeutic hypothesis for cancer treatment. Treatment of mouse cancer models with anti-CCR8 antibodies depleted intratumoral Treg cells and reduced tumor growth.^{7,8} Furthermore, anti-CCR8 treatment can synergize with anti-PD-1 treatment in anti-PD-1-susceptible and -resistant cancer models, highlighting the therapeutic potential of anti-CCR8 antibodies.

SRF114 is a fully human, afucosylated anti-CCR8 antibody designed to preferentially deplete CCR8⁺ Treg cells within the tumor microenvironment. Here, we explore the ability of SRF114 to activate effector immune cells associated with ADCC and ADCP, deplete Treg cells, and reduce tumor growth in a mouse cancer model.

Methods Surface expression of CCR8 on human intratumoral and peripheral immune cells was characterized by flow cytometry. Human peripheral blood mononuclear cells (PBMCs) and dissociated tumor cells (DTCs) were cultured with SRF114 to examine immune cell activation and Treg cell depletion. The efficacy of SRF114 was assessed in MC38 tumor-bearing human CCR8 knock-in (hCCR8 KI) mice.

Results CCR8 surface expression was highest on intratumoral Treg cells compared with peripheral Treg cells and other immune cells. In PBMC cultures, Fc gamma receptor (FcγR)-expressing cells, including natural killer (NK) cells and monocytes, exhibited dose-dependent activation from SRF114 bound to CCR8⁺ cells. DTC cultures treated with SRF114 also displayed dose-dependent NK cell activation and selective Treg cell depletion, with marginal impacts on effector T cell populations. The potency of SRF114 to activate FcγR⁺ cells in DTCs was enhanced compared with that in PBMCs due to increased CCR8 expression on Treg cells. In a syngeneic tumor model, hCCR8 KI mice treated with SRF114 exhibited a significant reduction in tumor growth and depletion of intratumoral Treg cells, with minimal impact on their peripheral counterparts.

Conclusions SRF114 can induce ADCC and/or ADCP pathways to deplete CCR8⁺ Treg cells in vitro. Demonstrated depletion of intratumoral Treg cells and reduction of tumor growth in vivo support SRF114 as a therapeutic candidate to deplete intratumoral Treg cells and drive antitumor immunity in human cancer patients.

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