Background Chimeric antigen receptor (CAR)-T cells for solid tumors have shown modest effectiveness as compared to hematologic malignancies, a consequence of antigen heterogeneity, the immuno-suppressive tumor microenvironment (TME), limited cell persistence, and perhaps most notably, the trafficking of the CAR-T cell to the tumor itself. Early detection of CAR-T cells within a solid tumor has been associated with better outcomes across several clinical trials in diverse tumor settings, suggesting that strategies focused on enhancing CAR-T cell homing to and infiltration into the tumor can yield therapeutic benefit.

Methods Here, we demonstrate that following irradiation or exposure to common chemotherapy drugs, selected tumor cell lines (breast, ovarian, and prostate) specifically upregulate several chemokines, notably the CXCR2 ligand, interleukin (IL)-8, up to 4-fold over baseline control (e.g. 24ng/ml increased to 79ng/ml for SKOV3; 2.9ng/ml increased to 12.5ng/ml for MDA-MB-231). To leverage the upregulation of IL-8 as a mechanism of directing CAR-T cells to the tumor site, we initially engineered primary CAR-T cells to express CXCR2 and demonstrated functional migration, in a dose-dependent manner, to recombinant IL-8 in an in vitro transwell chemotaxis assay; maximal migration of approximately 2-fold over baseline was observed with 10ng/ml of rhIL-8. Similarly, supernatant from pre-conditioned tumor lines also elicited functional enhancements in migration (up to 4-fold specific migration).

In addition, ovarian tumors were sub-optimally treated with paclitaxel in vivo, which promoted infiltration of CXCR2+ CAR-T cells and demonstrated enhanced tumor control.

Results We then incorporated these findings into our off-the-shelf, iPSC-derived CAR-T cell product platform. Induced pluripotent stem cells (iPSCs) were precisely engineered to co-express CAR and CXCR2 and subsequently differentiated to T cells to generate iPSC-derived CAR-T cells (CAR-iT cells). Like their primary CAR-T cell counterparts, functional chemotaxis of CXCR2+ CAR-iT cells was also observed in response to recombinant IL-8 and preconditioned tumor media. Importantly, CXCR2 expression did not limit CAR-dependent cytolitic function and the specificity of CAR-iT cells, underscoring the compatibility of this approach. Further in vitro and in vivo studies are ongoing and will be presented.

Conclusions Collectively, these data demonstrate that rational engineering of unique chemokine receptors to deliver the ideal chemokine/chemokine receptor match between tumors and effector cells can be leveraged to enhance tumor targeting and trafficking of CAR-iT cells for more effective treatment of solid tumors.

Ethics Approval These studies were approved by Fate Therapeutics Institutional Animal Care and Use Committee and were carried out in accordance with the National Institutes of Health’s Guide for the Care and Use of Laboratory Animals.

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