121 ICAM-1-SPECIFIC AFFINITY TUNED CAR T CELLS EXPRESSING SSTR2 FOR REAL-TIME IMAGING

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Background The use of CAR T cells for solid tumors has a number of challenges, such as lack of tumor-specific targets, CAR T cell exhaustion, and the immunosuppressive tumor microenvironment. To address these challenges, AffyImmune has developed technologies to affinity tune and track CAR T cells in patients. The targeting moiety is affinity tuned to preferentially bind to tumor cells overexpressing the target while leaving normal cells with low basal levels untouched, thereby increasing the therapeutic window and allowing for more physiological T cell killing. The CAR T cells are designed to express SSTR2 (somatostatin receptor 2), which allows for the tracking of CAR T cells *in vivo* via PET/CT scan using FDA-approved DOTATATE.

Methods AIC100 was generated by affinity tuning the I-domain of LFA-1, the physiological ligand to ICAM-1. Various mutants with 10^6-fold difference in affinity were evaluated for affinity. This allowed structure activity relationships to be conducted using CAR T cells expressing the various affinity mutants against targets with varying antigen densities. The variant with micromolar affinity was clearly the most effective in non-clinical animal models. AIC100 is currently being evaluated to assess safety, CAR T expansion, tumor localization, and preliminary activity in patients with advanced thyroid cancer in a phase I study (NCT04420754). Our study uses a modified toxicity probability interval design with three dosage groups of 10 x 10^6, 100 x 10^6, and 500 x 10^6 cells.

Results Preclinical studies demonstrated greater *in vivo* anti-tumor activity and safety with lower affinity CAR T cells. A single dose of AIC100 resulted in tumor elimination and significantly improved survival of animals. AIC100 activity was confirmed in other high ICAM-1 tumor models including breast, gastric, and multiple myeloma. In a Phase I patient given 10-million CAR T cells, near synchronous imaging of FDG and DOTATATE revealed preliminary evidence of transient CAR T expansion and tumor reduction at multiple tumor lesions, with the peak of CAR T density coinciding with the spike in CAR T numbers in blood.

Conclusions We have developed affinity tuned CAR T cells designed to selectively target ICAM-1 overexpressing tumor cells and to spatiotemporally image CAR T cells. Near-synchronous FDG and DOTATATE scans will enhance patient safety by early detection of off-tumor CAR T activity and validation of tumor response. We anticipate that our 'tune and track' technology will be widely applicable to developing potent yet safe CAR T cells against hard-to-treat solid cancers.

Trial Registration NCT04420754

Ethics Approval

IRB number 19-12021154IACUC (animal welfare): All animal experiments were performed in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals. Animal handling protocols were approved by the Institutional Laboratory Animal Use and Care Committee of Weill Cornell Medicine (Permit Number: 2012–0063).

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