Efficacy of αβT cell based immunotherapies relies on CCR5 expression in both CD4+ and CD8+ αβT cells

In this study we explore strategies to improve αβT cell infiltration within the tumor microenvironment (TME) in order to boost the efficacy of adoptive αβT cell therapies in various malignancies. Infiltration of tumor-reactive αβT cells, especially CD8+ αβT cells, correlates with improved clinical outcomes and responses to immunotherapies.

We used in vitro models, in which we examined the infiltration of BCMA-targeting CAR αβT cells (BCMA-CART) and BTN2/3-targeting γδTCR (TEG) engineered αβT cells and screened the supernatant for the presence of soluble factors. After identifying possibly relevant factors, we blocked these in further in vitro models to examine their relevance for αβT cell migration and αβT cell specific killing. In the following, we overexpressed CCR5 in the αβT cells used in the in vitro models and investigated the effect of CCR5 overexpression on αβT cell migration and αβT cell specific killing.

In the used *in vitro* models, we examined the infiltration of BCMA-targeting CAR αβT cells (BCMA-CART) and BTN2/3-targeting γδTCR (TEG) engineered αβT cells, finding that αβT cell infiltration was limited; particularly in the CD8+ T lymphocyte compartment. Chemokines including CCL4 were found to be essential for αβT cell migration in the TME, with blocking of these chemokines showing a reduction in αβT cell migration and tumor-specific killing. Furthermore, overexpressing the corresponding chemokine receptor CCR5 in tumor-reactive αβT cells significantly improved infiltration capacity and tumor targeting of engineered immune cells.

This study highlights the importance of improving αβT cell infiltration for αβT cell therapies and argues for the potential of CCR5 overexpression in CD8+ αβT cells for improving clinical outcomes, particularly in the treatment of solid malignancies.