

BIO_02 - Anti-CAIX CAR T cells in the treatment of renal cell carcinoma patient-derived xenografts

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Introduction: T cells expressing chimeric antigen receptors (CAR T cells) have demonstrated remarkable clinical efficacy in treating different hematologic tumors. However, several challenges must be overcome to allow similar efficiency against solid tumors. Several hypoxic tumors and especially clear cell renal carcinoma (ccRCC) express high amounts of an enzyme called carbonic anhydrase IX (CAIX), which is considered an interesting tumor-associated antigen for CAR T cell development.

Objectives: This project aims the evaluation of anti-tumor effects of CAIX-targeted CAR T cells containing CD28 or 4-1BB as costimulatory domains and capable of inducing different levels of T cell exhaustion in a ccRCC patient-derived xenograft model (PDX).

Methodology: The lentiviruses will be produced by transient transfection, concentrated, titrated, and transduced into T cells CD4:CD8 2:1 purified from the mononuclear fraction of the blood of healthy donors. The resulting CAR T cells will be expanded, and their transduction levels will be accessed in the short and long term. The Anti-CAIX CAR T cells containing different co-stimulatory domains CD28 or 4-1BB will be evaluated *in vivo* in a ccRCC PDX model, determining the exhaustion status of tumor-infiltrating T cells.

Results: Using two doses of $\cong 10^6$ CAR T cells/kg dose, Anti-CAIX 4-1BB resulted in smaller tumors with slightly higher survival rates. However, the anti-CAIX construct with CD28 was unique in avoiding the occurrence of metastasis and significantly reduced the T cell population expressing all of the exhaustion markers analyzed. No significant difference in the expression of alanine transaminase (ALT), aspartate transaminase (AST) and creatinine was found among the groups, providing further evidence for the absence of hepatic and nephrotoxicity.

Conclusion: This project has the potential to optimize the performance of CAR T against ccRCC.

Keywords: CAR T; Solid tumors; Carbonic anhydrase IX; Renal carcinoma