CAR-T cells harboring a camelid single domain antibody as a targeting agent to CEACAM6 antigen in pancreatic cancer

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INTRODUCTION

Modulation of the immune system is showing tremendous promise in the treatment of malignancies. In addition to checkpoint inhibitors that re-activate T cells present in the tumor microenvironment, exogenously transduced chimeric antigen receptor (CAR) T cells are providing excellent responses in clinical trials for the treatment of leukemias. To date, the most beneficial CAR-T therapies have been directed against hematological cancers, with less success observed against solid tumors.

Carcinembryonic Antigen Related Cell Adhesion Molecule 6 (CEACAM6) is overexpressed in many types of human cancers such as breast, pancreatic, colorectal, and non-small-cell lung adenocarcinoma, and is an independent predictor of overall survival and disease free survival. Targeting this molecule by antibodies has slowed tumor progression in certain animal models. 2A3 is a camelid single domain antibody isolated from a whole cancer cell-immunized llama library. The antibody binds specifically to the CEACAM6 antigen with high affinity (3nM as measured by surface plasmon resonance) and inhibits the proliferation of CEACAM6-expressing cancer cells in vivo.

In this study, we investigated the use of CAR-T cells as a therapy for pancreatic carcinoma. CAR-T cells were engineered to express the anti-CEACAM 6 antibody 2A3 in combination with the CD28 costimulatory molecule and CD3 zeta chain. Co-incubation of anti-CEACAM6 CAR-T cells with the CEACAM6-expressing pancreatic cancer cell line BxPC3 resulted in decreased viability of the BxPC3 cells and T cell production of cytokines (IL-2 and IFNγ), suggesting potential anti-cancer activity of the anti-CEACAM6 CAR-T cells.

The efficacy of anti-CEACAM6 CAR-T cells in vivo was investigated in two xenograft models using BxPC3 tumor cells. In the first study, treatment with anti-CEACAM6 CAR-T cells was initiated on the day after tumor implantation. In the second study, tumors were allowed to reach a volume of 100mm³ before treatment was initiated. In both studies, treatment with anti-CEACAM6 CAR-T cells significantly decreased the growth of the BxPC3 tumors as compared to treatment with untransduced T cells. The results strongly support the use of anti-CEACAM6 CAR-T cells as an immunotherapeutic agent against CEACAM6-expressing solid cancers, and that camelid single domain antibodies can be easily adopted for CAR-T therapies.

ACKNOWLEDGMENTS

The authors would like to thank ProMab Biotechnologies, Inc. for performing the studies described in this poster.

RESULTS

Expression of the 2A3 llama anti-CEACAM6 antibody by CAR-T cells

Cell viability of BxPC3 cells treated with anti-CEACAM6 CAR-T cells generated from three different donor PBMCs

Cytokine production from anti-CEACAM6 CAR-T cells incubated with BxPC3 cells

Efficacy of anti-CEACAM6 CAR-T cells in a BxPC3 preventative xenograft model

Efficacy of anti-CEACAM6 CAR-T cells in a BxPC3 treatment xenograft model

CONCLUSIONS

- CAR-T cells generated against the CEACAM6 antigen are highly effective at reducing the cell viability of the CEACAM6-expressing pancreatic cancer cell line BxPC3 in vivo.
- CAR-T cells generated against the CEACAM6 antigen significantly reduce the growth of the BxPC3 pancreatic carcinoma in vivo both when used in a preventative tumor model and in a model where treatment is initiated after the tumor is established.
- Camelid single chain antibodies can be easily adopted for use in CAR-T therapies.

REFERENCES
