

Importantly, TAC-engineered gamma/delta T cells displayed robust cytotoxicity at very low effector:target ratios (<1) and caused regression of human tumor xenografts that were otherwise resistant to non-engineered gamma/delta T cells. Curiously, gamma/delta T cell manufacturing was sensitive to the quality of the lentivirus product, where products with low titers were associated with outgrowth of conventional alpha/beta T cells. Outgrowth of alpha/beta T cells was not observed with gamma-retroviruses. We are presently evaluating the anti-tumor activity of gamma-retrovirus-engineered gamma/delta T cells.

Conclusions Off-the-shelf engineered gamma/delta T cells represent a strategy to reduce manufacturing cost and may represent the next generation of engineered T cell therapies. TAC receptors provide a robust tool for directing gamma/delta T cells to attack tumors that are otherwise resistant to gamma/delta T cells and should be evaluated further.

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Ethics Approval The study was approved by McMaster's Animal Research Ethics Board, AUP#19-02-10.

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CORD-BLOOD DERIVED NK CELLS, AND CAR-T CELLS, AN ATTRACTIVE IMPROVED IMMUNOTHERAPY TREATMENT TO BE CONSIDERED FOR HEMATOLOGICAL MALIGNANCIES

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Background Multiple myeloma (MM) remains an incurable hematological malignancy where a proportion of patients relapse or become refractory to current treatments. Administration of autologous T cells modified with a chimeric antigen receptor (CAR) against B cell maturation antigen (BCMA) has achieved high percentages of complete responses. Unfortunately, the lack of persistence of CART-BCMA cells in the patient leads to relapses. On the other side, cord-blood derived natural killer cells (CB-NK) is an off-the-shelf cellular immunotherapy option to treat cancer patients with high potential due to their anti-tumor activity. However, clinical results in patients up to date have been sub-optimal. Whereas CB-NK are innate immune cells and their anti-tumor activity is developed in a few hours, CART cells are adaptive immune cells and their activity develops at later time points. Moreover, we previously described that CB-NK secrete inflammatory proteins that promote the early formation of tumor-immune cell clusters bringing cells into close contact and thus, facilitating the anti-tumor activity of T cells. Therefore, we hypothesized that the addition of a small number of CB-NK to CART cells would improve the anti-tumor activity and increase the persistence of CART cells.

Methods T cells transduced with a humanized CAR against BCMA and CB-NK were employed at 1:0.5 (CART:CB-NK) ratio. Cytotoxicity assays, activation markers and immune-tumor cell cluster formation were evaluated by flow cytometry and fluorescence microscopy. In vivo models were performed in NSG mice.

Results The addition of CB-NK to CART cells demonstrated higher anti-MM efficacy at low E:T ratios during the first 24h and in long-term cytotoxicity assays, where the addition of CB-NK to CART cells achieved complete removal of tumor cells. Analysis of activation marker CD69 and CD107a degranulation from 4h to 24h of co-culturing proved differences only at 4h, where CD69 and CD107a in CART cells were increased when CB-NK were present. Moreover, CB-NK accelerated an increased formation of CART-tumor cell clusters facilitating the removal of MM cells. Of note, CB-NK addition did not increase total TNF α and IFN γ production. Finally, an in vivo model of advanced MM with consecutive challenge to MM cells evidenced that the addition of CB-NK achieved the highest efficacy of the treatment.

Conclusions Our results suggest that the addition of 'off-the-shelf' CB-NK to CART cells leads to a faster and earlier immune response of CART cells with higher long-term maintenance of the anti-tumor response, suggesting this combinatorial therapy as an attractive immunotherapy option for MM patients.

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INCLUSION OF A DAP10 COSTIMULATORY DOMAIN ENHANCES ANTI-TUMOR EFFICACY OF CHIMERIC PD1-EXPRESSING T CELLS IN MULTIPLE TYPES OF SOLID TUMORS

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Background Adoptive transfer of T cells is a promising anti-tumor therapy for many cancers. To enhance tumor recognition by T cells, chimeric antigen receptors (CAR) consisting of signaling domains fused to receptors that recognize tumor antigens can be expressed in T cells. One receptor that is a prospective target for a new chimeric antigen receptor is PD1 because the ligands for the PD1 receptor are expressed on many cancer types. Therefore, we developed a murine chimeric PD1 receptor (chPD1) consisting of the PD1 receptor extracellular domain and the activation domain of CD3 zeta. In addition, current chimeric antigen receptor therapies utilize various costimulatory domains to enhance anti-tumor efficacy. Therefore, we also compared the inclusion of CD28, Dap10, 4-1BB, GITR, ICOS, or OX40 costimulatory domains in the chPD1 receptor to determine which costimulatory domain induced optimal anti-tumor immunity.

Methods To determine if this novel CAR could potentially target a wide variety of tumors, the anti-tumor efficacy of chPD1 T cells against murine lymphoma, melanoma, kidney, pancreatic, liver, colon, breast, ovarian, prostate, and bladder cancer cell lines was measured.

Results Of the eighteen cell lines tested, all expressed PD1 ligands on their cell surface, making them potential targets for chPD1 T cells. Regardless of the costimulatory domain in the CAR, all of the chPD1 T cells induced similar levels of T cell proliferation and tumor cell lysis. However, differences were observed in the cytokine secretion profiles depending on which costimulatory receptor was included in the CAR. While