COMBINATION NK-92MI\textsuperscript{CD64} CELL THERAPY APPROACH WITH THERAPEUTIC ANTIBODIES TO TREAT METASTATIC PROSTATE CANCER

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Background Metastatic castration-resistant prostate cancer (mCRPC) is a lethal, heterogeneous disease that has been largely resistant to immunotherapy. The lack of efficacy is due, in part, to the immunosuppressive tumor microenvironment and new therapeutic strategies for mCRPC must stimulate an antitumor response in the immunologically ‘cold’ tumors. Combination therapies that target both the tumor stroma and cancer cells could overcome the limitations of current immunotherapies and are demonstrated to be effective in multiple cancer models.\textsuperscript{1,2} NK cells are being explored as cell therapies and targeting NK cells to solid tumors can be improved by engineering the effector cells to express CD64, a high-affinity Fc receptor for human IgG. CD64 can capture soluble antibodies with 30–100x higher affinity than CD16A and mediates cell killing when antibody is bound.\textsuperscript{3} This docking platform allows for switchable targeting elements to redirect NK cells to multiple tumor antigens and facilitates the development of combination cell therapies.

Methods NK-92MI\textsuperscript{CD64} cell therapy was evaluated in combination with antibodies targeting the prostate tumor antigen-associated calcium signal transducer 2 (TROP2) and the cancer-associated fibroblast (CAF) marker fibroblast activation protein alpha (FAP). Antibodies were bound to CD64 and effector cells (1:1 aTROP2 and aFAP mAb) were co-cultured with prostate cancer and CAF target cells (1:1 DU145 and hPrCSC-44 cells). Killing effect was measured using the DELFIA Cell Cytotoxicity assay and IFN-\(\gamma\) production was assessed by flow cytometry. Tumor-bearing NSG mice (DU145 and hPrCSC-44 cells; 100–200 mm\(^3\); N=4/group) received adoptive transfer of NK-92MI\textsuperscript{CD64} cells with or without bound antibodies (1 \times 10\(^7\) cells; 1:1 aTROP2 and aFAP mAb) or saline (s.c.; 1x/wk for 4 wks). Therapeutic efficacy was evaluated by measuring tumor volumes.

Results IFN-\(\gamma\) production was increased with the addition of TROP2- or FAP-targeted antibodies. Cytotoxicity of the combination therapy was two-fold higher than either monotherapy (ANOVA \(P=0.012\); figure 1) and six-fold higher than NK-92MI\textsuperscript{CD64} cells alone (ANOVA \(P=0.0018\); figure 1). The killing effect was lost when the antibodies were switched to an isotype control, indicating that the targeting mechanism is antigen dependent. Robust antitumor activity was demonstrated in vivo and the combination therapy significantly reduced tumor growth by 78\% compared to the saline control (ANOVA \(P=0.004\); figure 2).

Conclusions Our study suggests that NK-92MI\textsuperscript{CD64} cell therapy with antibodies targeting the tumor stroma and malignant cells is effective in a prostate cancer model. Validation of this combination therapy presents a new approach for treating mCRPC and could improve antitumor response.

Ethics Approval The study was approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC) approval number 1708A-35052.

REFERENCES
1. Fabre M, et al. OMTX705, a Novel FAP-Targeting ADC Demonstrates Activity in Chemotherapy and Pembrolizumab-Resistant Solid Tumor Models. Clin Can Res. 2020;26:3420–30.
2. Kakarla S, et al. Antitumor effects of chimeric receptor engineered human T cells directed to tumor stroma. Mol Ther. 2013;21:1611–20.
3. Snyder K, et al. Expression of a recombinant high affinity IgG Fc receptor by engineered NK cells as a docking platform for therapeutic mAbs to target cancer cells. Front Immunol 2018;9:2873.

ADOPTIVE T CELL THERAPY TARGETING SOMATIC P53 MUTATIONS

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Background Adoptive cell therapies (ACT) directed against the products of somatic mutations in cancer cells can lead to long lasting clinical responses. We focused on ACT against shared p53 mutations to be used to potentially treat a broad range of patients with common cancers. We have built a library of anti-mutant p53 T cell receptors (TCRs) to be used for the treatment of patients with epithelial cancers in the autologous setting and as ‘off-the-shelf’ reagents for patients sharing the same p53 mutation and HLA.

Methods Tumor infiltrating lymphocytes (TILs) were screened for recognition of p53 mutations and were expanded as previously described.\textsuperscript{1} For treatment of patient 4349 with metastatic breast cancer, the patient’s peripheral blood T cells were retrovirally engineered to express the allogeneic anti-p53 R175H TCR.

Results We identified TILs recognizing ‘hotspot’ p53 mutations, such as R175H, Y220C, and R273C as well as less frequent but recurrent mutations, such as L111R, C135Y, and Q331H (table 1). First, we adoptively transferred TILs that