Background In recent years, the FDA has approved engineered autologous T cell therapies with remarkable efficacy against hematological cancers. In addition, non-engineered tumor infiltrating lymphocyte (TIL) therapies have shown unprecedented benefit against solid tumors in early clinical trials. Despite their success, TIL products have limitations including the need for specialized surgery to obtain sterile tumor for T cells, low neoantigen breadth, and the potential for T cells that may be pro-tumor, exhausted, or not tumorspecific. These limitations may hinder efficacy and accessibility for certain patients. We have developed an autologous, peripheral blood-derived non-engineered T cell therapy, GEN-011, that embraces the advantages of TIL while improving on their limitations by targeting true tumor-specific neoantigens identified by the ATLAS™ bioassay and avoiding potentially pro-tumor Inhibigens.

Methods Peripheral blood mononuclear cells and a tumor biopsy are collected from each subject; tumor DNA is sequenced by WES. The ATLAS bioassay is used to individually screen each tumor mutation with the patient’s own T cells to identify neoantigen targets of pre-existing CD4+ and/or CD8+ T cell responses. The robust clinical scale manufacturing process, PLANET™, expands the patient’s peripheral blood T cells on ATLAS-identified stimulatory neoantigens.

Results The PLANET process produces GEN-011 drug products (DP) containing billions of antigen-specific, cytolytic T cells. Development and engineering runs using peripheral blood T cells from cancer patients and healthy donors resulted in DPs containing >97% T cells, >90% of which were central and effector memory phenotypes. A median 334-fold increase in antigen-specific T cells was observed in GEN-011 DPs over their starting frequency in peripheral blood with up to 67% of cells upregulating activation markers upon antigen recognition. Additionally, DP T cells secrete up to 50,000 pg/mL of IFN-gamma in response to antigen stimulation. In cancer patient samples, DPs respond to up to 89% of intended neoantigen targets compared to <10% reported recently for TIL products.

Conclusions GEN-011 is an autologous, neoantigen-specific T cell product, with key advantages over TIL therapy. First, GEN-011 has an unparalleled breadth of neoantigen coverage, targeting up to 30 relevant neoantigens with non-exhausted CD4+ and CD8+ memory T cells to overcome non-tumor specific ‘passenger’ T cells. Second, GEN-011 avoids pro-tumor Inhibigens that may be detrimental to clinical responses. Third, GEN-011 does not require extra surgery or viable tumor for manufacturing. In conclusion, GEN-011 is a first-in-class transformational T cell therapy candidate with characteristics that should improve accessibility and efficacy for patients with solid tumors.

Ethics Approval Informed consent was obtained from all individuals providing samples for this study.

REFERENCES
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. 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. 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$^{CD64}$ 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$^{CD64}$ 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 trop-2- 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$^{CD64}$ 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$^{CD64}$ 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


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Abstract 151 Figure 2

Adoptive NK-92MI$^{CD64}$ cell transfer in combination with TROP2- and FAP-targeted antibodies reduces tumor growth in mice.

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. 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