included T cells reactive to a p53 mutation in an autologous manner for the treatment of patients with metastatic epithelial cancers (n=12). Except for the two patients who exhibited an objective response (RECIST), most of the patients did not respond to the therapy, possibly due to low frequencies of anti-mutant p53 cells in the infusion product, exhausted phenotype, and/or poor persistence (table 2). To overcome these barriers to TIL treatment, we retrovirally transduced autologous peripheral blood T cells to express an allogeneic anti-mutant p53 TCR. We engineered the HLA-A*02:01-restricted anti-p53 R175H TCR into patient 4349’s lymphocytes (transduction efficiency of 64%) and saw less expression of exhaustion markers relative to the TIL infusion products (table 2). This patient with metastatic breast cancer was refractory to the six prior chemotherapy regimens. After the transfer of 5.3e10 cells, the patient experienced an objective partial response, showing regression by 55% of skin and mediastinal lesions for 7 months. The persistence of the infused T cells was higher than the other patients who received the TIL treatment (table 2).

Conclusions The library of anti-mutant p53 TCRs we have generated can potentially be used to treat ~6% of all cancer patients. We are pursuing the adoptive transfer of TILs against mutant p53 naturally occurring in the tumor or TCR-engineered cells using ‘off-the-shelf’ receptors against mutant p53.

Ethics Approval This study was approved by the Institutional Review Board (IRB) of the NCI, and the approval numbers are as follows: Protocol 10-C-0166 (TIL treatment); Protocol 18-C-0049 (allogeneic TCR engineered T cell therapy)

REFERENCE

NEO-PTC-01 (BNT-221), AN AUTOLOGOUS NEOANTIGEN-SPECIFIC T-CELL PRODUCT FOR ADOPTIVE CELL THERAPY OF METASTATIC MELANOMA
1Divya Lenkala*, 1Jessica Kohler, 1Brian McCarthy, 1Michael Nelson, 1Jonathan McGee, 1Daniel Kallin, 1Janani Sridar, 1Paul Turcott, 1Dewi Harjanto, 2Cynthia Nijenhuis, 2Joost Van Den Berg, 1Richard Gaynor, 1Marit Van Buuren.
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Background Neoantigens are tumor-specific antigens that are important in the anti-tumor immune response. These antigens are not subject to central immune tolerance and are therefore potentially more immunogenic than tumor-associated antigens. NEO-STIM®, our propriety ex vivo induction process, was developed to generate T-cell products specific to these neoantigens from the peripheral blood of patient. Here, we present the results of a proof of concept, pre-clinical study with multiple successful process engineering runs generating a neoantigen-specific T-cell product (NEO-PTC-01) using leukapheresis from metastatic melanoma patients. These products contain specific T-cell responses targeting multiple neoantigens from each individual patient’s tumor.

Methods Patient-specific neoantigens were predicted using our RECON® bioinformatics platform. Predicted high-quality neoantigens were utilized in our ex vivo stimulation protocol, NEO-STIM, in the process engineering runs generating a neoantigen-specific T-cell product (NEO-PTC-01) using leukapheresis from metastatic melanoma patients. These products contain specific T-cell responses targeting multiple neoantigens from each individual patient’s tumor.

Abstract 152 Table 1

<table>
<thead>
<tr>
<th>TCR source (patient ID)</th>
<th>p53 mutation</th>
<th>p53 mutation frequency (%)</th>
<th>HLA restriction</th>
<th>HLA frequency (%)</th>
<th>Potentially treatable patient with solid cancer (%)</th>
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</thead>
<tbody>
<tr>
<td>4141*</td>
<td>R175H</td>
<td>4.46</td>
<td>A02:01</td>
<td>47.4</td>
<td>2.088</td>
</tr>
<tr>
<td>4359</td>
<td>Y220C</td>
<td>1.521</td>
<td>A02:01</td>
<td>47.4</td>
<td>0.721</td>
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<tr>
<td>4146*; 4343</td>
<td>R273C</td>
<td>2.754</td>
<td>DRB1*04:02</td>
<td>24.2 (60-80%) in Hispanic populations, ~20% in American and Asian populations)</td>
<td>0.666</td>
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<tr>
<td>4146*; 4343</td>
<td>Y220C</td>
<td>1.521</td>
<td>DRB3*02:02</td>
<td>32.8</td>
<td>0.499</td>
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</table>

Abstract 152 Table 2

<table>
<thead>
<tr>
<th>Cell product</th>
<th>Phenotypic profile</th>
<th>HLA restriction</th>
<th>CD3+</th>
<th>CD8+</th>
<th>CD4+</th>
<th>CD16+CD56+</th>
<th>Anti-mutant TCRs</th>
<th>CD3+CD8+ killing capacity</th>
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<tr>
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<td></td>
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<tr>
<td>NeoStim-01</td>
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Abstracts
Results Here we present the successful induction of 4-5 CD8\(^+\) and 4-7 CD4\(^+\) T-cell responses per patient, generated using peripheral blood mononuclear cells from multiple melanoma patients during these successful process engineering runs. We then extensively characterized these T-cell responses and demonstrate that these responses are functional, specific and have cytolytic capacity. Moreover, the induced T cells can recognize autologous tumor.

Conclusions NEO-STM is a novel platform that generates ex vivo T-cell responses to high-quality neoantigen targets. NEO-PTC-01, the neoantigen-specific T cell product generated from this process, is a potent adoptive cell therapy targeting multiple immunogenic neoantigens in patients with metastatic melanoma.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0153

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**REFERENCES**


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**Abstracts**

**Marrow-Infiltrating Lymphocytes (MILs): A Novel Adapting Immunotherapy for Hematological and Solid Tumors**


**Background**

Marrow infiltrating lymphocytes (MILs\(^{TM}\)) are the product of activating and expanding bone marrow T cells. The bone marrow is a specialized niche in the immune system enriched for antigen-experienced, memory T cells. In patients with multiple myeloma and other hematological malignancies that relapse post-transplant, MILs have been shown to contain tumor antigen-specific T cells and adoptive cell therapy (ACT) using MILs has demonstrated antitumor activity. The bone marrow has been shown to harbor tumor-antigen specific T cells in patients with melanoma, glioblastoma, breast, non-small-cell lung and pancreatic cancers. Here, we sought to determine if tumor-specific MILs could be expanded from the bone marrow of patients with a range of different solid tumors.

**Methods**

Bone marrow and blood samples were collected from patients with advanced and metastatic cancers. To date, samples have been collected from a minimum of four patients with non-small cell lung cancer (NSCLC), prostate cancer, head and neck cancer, glioblastoma, and breast cancer. Samples from patients with multiple myeloma were used as a reference control. Utilizing a 10-day proprietary process, MILs and peripheral blood lymphocytes (PBLs) were activated and expanded from patient bone marrow and blood samples, respectively. T cell lineage-specific markers (CD3, CD4 and CD8) were characterized by flow cytometry pre- and post-expansion. Tumor-specific T cells were quantitated in expanded MILs and PBLs using a previously described cytokine-secretion assay. Briefly, autologous antigen-presenting cells (APCs) were pulsed with lysates from allogeneic cancer cell lines and co-cultured with activated MILs or PBLs. APCs pulsed with irrelevant mis-matched cancer cell line lysates or media alone were used as negative controls. Tumor-specific T cells were defined as the IFNgamma-producing population by flow cytometry.

Results MILs were successfully expanded from all patient bone marrow samples tested, regardless of tumor type. Cytokine-producing tumor-specific CD4\(^+\) and CD8\(^+\) T cells were detected in each of the expanded MILs. In contrast, tumor-specific T cells were not detected in any of the matched activated and expanded PBLs.

**Conclusions**

MILs have been successfully grown for all solid tumor types evaluated, including NSCLC, prostate, head and neck, glioblastoma and breast cancer. Clinical studies have been completed in patients with multiple myeloma and other hematological cancers. A phase IIa trial to evaluate MILs in combination with a checkpoint inhibitor is underway in patients with anti-PD1/PDL1-refractory NSCLC (ClinicalTrials.gov Identifier: NCT04069936). The preclinical data presented herein demonstrate that expanding MILs is feasible. MILs-based therapies hold therapeutic promise across a wide range of tumor indications.

**Ethics Approval**

This study was approved by each participating institution’s IRB.

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**IPSC-Derived NK Cells Mediate Robust Anti-Tumor Activity Against Glioblastoma**


**Background**

Gliomas represent the most common brain tumors within the central nervous system, with glioblastoma being the most aggressive type. Conventional treatment combines several approaches including surgery, chemotherapy, and radiation. However, the prognosis for glioblastoma remains unfavorable, with only 5% of patients surviving more than 5 years post-diagnosis. Thus, new treatment approaches are urgently needed. Natural killer (NK) cells directly lyse malignantly transformed or virally infected cells and secrete inflammatory cytokines that polarize cytotoxic immunity. Allogeneic