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 lytic capacity. Moreover, the induced T cells can recognize autologous tumor.

Conclusions NEO-STIM 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.

References

Background Marrow infiltrating lymphocytes (MILs) 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 mismatched 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.

References
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NK cell adoptive transfer has shown clinical benefit in patients with advanced cancer. However, limitations of this approach include relatively low numbers of donor NK cells that can be isolated during an apheresis and variability in the quality of NK cells between donors. To overcome these limitations, we have developed a GMP manufacturing strategy to mass produce NK cells from induced pluripotent stem cells (iPSCs) as an approach to off-the-shelf cancer immunotherapy.

We refer to these cells as ‘iNK’ (iPSC-derived NK) cells. Here, we provide preclinical data demonstrating the efficacy of iNK cells for immunotherapy against glioblastoma.

Conclusions iNK cells are highly cytotoxic against glioblastoma cells, and our preclinical in vivo data provides proof-of-concept for future clinical trials.

Ethics Approval This project has been approved by the University of Minnesota IACUC. Approval ID: 1812-36595A

REFERENCES


156 DISCOVERY OF TSC-100: A NATURAL HA-1-SPECIFIC TCR TO TREAT LEUKEMIA FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION THERAPY

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Background Approximately 30–40% of AML patients relapse following allogeneic hematopoietic stem cell transplantation therapy, leaving them with very few treatment options. Rare patients that naturally develop an HA-1-specific graft-versus-leukemia T cell response, however, show substantially lower relapse rates. HA-1 (VHHDLLLEA, genotype RS_1801284 A/G or A/A) is an HLA-A*02:01-and hematopoietically restricted minor histocompatibility antigen, making it an ideal candidate for TCR immunotherapy for liquid tumors.