A POTENT AND OFF-THE-SHELF ONK CELL THERAPY RESPONSE IN MELANOMA IS MEDIATED BY STEM-LIKE CD8 T CELLS

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Background Adoptive T cell therapy (ACT) utilizing ex vivo-expanded autologous tumor infiltrating lymphocytes (TILs) can result in complete regression of human cancers.1 Successful immunotherapy is influenced by several tumor-intrinsic factors.2–5 Recently, T cell-intrinsic factors have been associated with immunotherapy response in murine and human studies.4 5 Analyses of tumor-reactive TILs have concluded that antitumor neoantigen-specific TILs are enriched in subsets defined by the expression of PD-1 or CD39.6–7 Thus, there is a lack of consensus regarding the tumor-reactive TIL subset that is directly responsible for successful immunotherapies such as ICB and ACT. In this study, we attempted to define the fitness landscape of TIL-enriched infusion products to specifically understand its phenotypic impact on human immunotherapy responses.

Methods We compared the phenotypic differences that could distinguish bulk ACT infusion products (I.P.) administered to patients who had complete response to therapy (complete responders, CRs, N = 24) from those whose disease progressed following ACT (non-responders, NRs, N = 30) by high dimensional single cell protein and RNA analysis of the I.P. We further analyzed the phenotypic states of anti-tumor neoantigen-specific TILs from patient I.P (N = 26) by flow cytometry and single cell transcriptomics.

Results We identified two CD8+ TIL populations associated with clinical outcomes: a memory-progenitor CD39-negative stem-like TIL (CD39-D69-) in the I.P. associated with complete cancer regression (overall survival, P < 0.0001, HR = 0.217, 95% CI 0.101 to 0.463) and TIL persistence, and a terminally differentiated CD39-positive TIL (CD39+D69+) population associated with poor TIL persistence post-treatment. Although the majority (>65%) of neoantigen-reactive TILs in both responders and non-responders to ACT were found in the differentiated CD39+ state, CR infusion products also contained a pool of CD39- stem-like neoantigen-specific TILs (median = 8.8%) that was lacking in NR infusion products (median = 23.6%, P = 1.86 x 10-5). Tumor-reactive stem-like T cells were capable of self-renewal, expansion, and persistence, and mediated superior anti-tumor response in vivo.

Conclusions Our results support the hypothesis that responders to ACT received infusion products containing a pool of stem-like neoantigen-specific TILs that are able to undergo prolific differentiation state and enrich cellular stemness.2 This would enhance TILs in vivo anti-tumor activity and prolong their survival. Elucidating TILs and their relations with tumor’s PD-L1 expression would allow clinicians to appropriately recognize sarcoma’s tumor immune environments and select the most desirable infiltrates for superior ACT.

Ethics Approval The study was approved by Mount Sinai Hospital’s Ethics Board, approval number 01-0138-U.

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expansion, give rise to differentiated subsets, and mediate long-term tumor control and T cell persistence, in line with recent murine ICB studies mediated by TCF+ progenitor T cells.\(^4\)\(^5\) Our data also suggest that TIL subsets mediating ACT-response (stem-like CD39-) might be distinct from TIL subsets enriched for anti-tumor-reactivity (terminally differentiated CD39+) in human TIL.\(^6\)\(^7\)

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**Trial Registration NA**

**Ethics Approval** The study was approved by NCI’s IRB ethics board.

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**Abstract 774 Figure 1**  Antibiotics up to six months before ICI reduce OS

**Figure 1**: Antibiotics Prior to Checkpoint Inhibitor Therapy Lead to Inferior Overall Survival: Analysis of patients treated with any type of antibiotic lead to worsened overall survival compared to those who did not receive antibiotics or who received a one time dose of cefazolin. Statistical analysis showed by both Log Rank and Wilcoxon testing p-values were <0.0001 with median survival 6.5y vs. 2.3y for those who received antibiotics prior to ICI treatment (HR 3.4, 95% CI 2.2 to 5.3).

**Abstract 774 Figure 2**  Antibiotics up to six months before ICI reduce PFS

**Figure 2**: Antibiotics Prior to Checkpoint Inhibitor Therapy Lead to Inferior Progression-Free Survival: Analysis of patients treated with any type of antibiotic lead to worsened progression-free survival as well compared to those who did not receive antibiotics or who received a one time dose of cefazolin. Statistical analysis showed by both Log Rank and Wilcoxon testing p-values were 0.0027 and 0.0011 respectively. Median PFS from initiation of immunotherapy was 1.1y vs. 0.46y for those who received antibiotics prior to ICI treatment (HR 1.7, 95% CI 1.2 to 2.5).