Discovery of novel MAGEC2 epitopes for TCR-T adoptive cell therapy from expanded T cell clones of TIL therapy products

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Overview of Study

Background: TCR-T adoptive cell therapy is a promising approach to treating solid tumors, but the heterogeneous expression of TCR targets by the tumor and T cell evasion mechanisms are barriers to durable responses. HLA heterogeneity further limits the addressable population. Multiplexing TCR-T products offers a unique strategy to address the heterogeneous landscape of targets presented by a diverse array of HLAs. In this study, we expanded the repertoire of novel epitopes presented on unadressed HLAs. TScan’s proprietary platform, TargetScan, is an unbiased method to discover the natural targets of T cell clones responding to tumors.

Methods: The target landscape recognized by the most expanded T cell clones derived from clinical melanoma TIL therapy products was evaluated using TScan’s TargetScan platform. TCR Targets were identified using a strategy of screening TCRs from the most expanded T cell clones against a peptide-library-wide, and the next most frequent T cell clones against a focused cancer tests antigen (CTA) library. Using this approach, TCRs recognizing targets with a favorable tissue expression profile of targeting with a TCR-T therapy were identified. Individual TCRs were cloned and evaluated for cytotoxicity, cytokine release, and T cell proliferation in response to co-culture with cancer cell lines expressing their cognate antigens.

Results: Peptide-wide screens of the 10 most expanded TCRs identified several known targets including the A*02:01 presented MART126-35 epitope as well as previously unknown cancer associated targets with limited tissue specific off-tumor expression including brain tissue. CTA focused screens identified novel targets including a novel clinically relevant B*07:02 presented epitope of the cancer targets antigen MAGEC2. The reactive TCR was identified and exhibited cytotoxicity, cytokine release, and T cell proliferation when co-cultured with B*07:02 expressing cancer cell lines that express MAGEC2 including FTC133, A101D, and SKLM81. The degree of the response corresponded with the level of MAGEC2 expression in the cell lines.

Conclusion: Using our TargetScan platform, we have shown that expanded T cell clones from clinical TIL products express TCRs that recognize tumor associated antigens; the novel B*07:02 restricted epitope of MAGEC2 is a promising target for TCR-T therapy potentially enabling us to target 20% of the US population. TargetScan mediated discovery of novel epitopes across a diverse set of HLAs will further enable a multiplexing approach to TCR-T therapy.

TargetScan platform enables the identification of the natural targets of TCRs

TargetScan screens revealed multiple targets of TIL therapy TCRs

Novel epitopes are immunogenic and recognized by the patient-derived TCR

TCRs sequences were sourced from TIL therapy products used to treat melanoma patients

Target expression profile in cancer and normal tissues

A) Tissue expression of TCR targets identified by TargetScan. Each square depicts the mean of the top quartile of the indicated tissue type. Targets ranged from established melanocyte antigen (MLANA), cancer tests antigen (MAGEC2), targets with limited tissue expression (ICAM5, NRCAM, COPG2), and ubiquitous tissue expression (A24, SH2B3). MAGEC2 exhibited a favorable tissue expression for TCR targeting and was evaluated further. B) pTCR illustrating MAGEC2 expression in melanoma cancer tissues of various progression showing increasing MAGEC2 expression with disease progression.

A) Schematic illustrating the screening strategy for the TCR repertoire from LA4. The TCR repertoire of the LA4 TIL product was cloned and transduced into donor T cells for screening against a CTA focused library. B) Screen results of LA4 TCRs illustrating a novel MAGEC2 epitope presented on HLA-A*2402. C) Flow cytometry analysis of LA4 TCRs recognizing MAGEC2 expressing cell line and cell lines with various expression of MAGEC2 was t-tested to express A2402.