DISCOVERY OF A NOVEL MAGEC2 EPITOPE FOR TCR-T ADOPTIVE CELL THERAPY FROM EXPANDED T CELL CLONES OF TIL THERAPY PRODUCTS

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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 but requires the identification of novel epitopes presented on unaddressed 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 peptidome wide library, and the next most frequent T cell clones against a focused cancer testis antigen (CTA) library. Using this approach, TCRs recognizing targets with a favorable tissue expression profile for 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 Peptidome wide screens of the 10 most expanded TCRs revealed 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 testis antigen MAGEC2. The reactive TCR was identified and exhibited cytotoxicity, cytokine release, and T cell proliferation when co-cultured with B*07:02 expressing cells including a thyroid cancer cell line FTC133 and melanoma cell lines A101D and SKLMS1 with the degree of the response corresponding to the level of MAGEC2 expression in the cell lines.

Conclusions Using our TargetScan platform, we have shown that expanded T cell clones from clinical TIL products express TCRs that recognize tumor associated targets; 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 patient population. TargetScan mediated discovery of novel epitopes across a diverse set of HLAs will further enable a multiplexing approach to TCR-T therapy.

Ethics Approval Data presented in this abstract used deidentified human materials and do not meet the definition for human subjects research.

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