390 DISCOVERY OF MAGE-A1-SPECIFIC TCR-T CELL THERAPY CANDIDATES TO EXPAND MULTIPLEX THERAPY OF SOLID TUMORS

Jenny Tadros*, Nancy Nabilsi, Mollie Jurewicz, Akshat Sharma, Kenneth L Jahan, Nicolas Gaspar, Kimberly M Cirelli, Teagan Parsons, Shazad A Khokhar, Shubhangi Kamalia, Sveta Padmanabhan, Badr Kiaf, Ribhu Nayar, Victor Ospina, Alok Das Mahopatra, Tary Traore, Antoine J Boudot, Livio Dukaj, Jin He, Ryan E Kritzer, Alexander Cristofaro, Chandan K Pavuluri, Emily Miga, Qikai Xu, Yifan Wang, Cagan Gurer, Gavin MacBeath. *TScan Therapeutics, Waltham, MA, USA*

Background Engineered T cell therapy holds great promise for treating solid tumors. To date, clinical investigations of TCR-T cell therapies have targeted one antigen/HLA at a time and have produced encouraging but partial response rates with limited durations. While heterogeneity of antigen expression is appreciated as a likely driver of patient relapse, the contribution of HLA loss of heterozygosity (LOH), occurring in up to 40% of tumors, is only now gaining attention. To address both antigen heterogeneity and HLA LOH requires a collection of TCRs recognizing multiple targets presented on multiple HLAs. MAGE-A1 is a cancer-testes antigen previously identified as the target of expanded tumor infiltrating T-cells using TScan's screening technology. Currently, TScan has two MAGE-A1-TCR-T products, recognizing epitopes on A*02:01 and C*07:02 approved for clinical development. Here we report discovery and lead selection of a MAGE-A1 TCR recognizing an epitope on A*01:01 (~24% population frequency).

Methods We discovered TCRs specific for an A*01:01-restricted MAGE-A1-derived epitope using TScan's proprietary ReceptorScan platform. Using an activation-based screening technology termed ActivScan, we screened a library of MAGE-A1-specific TCRs to select for greatest avidity and expression. These TCRs were functionally characterized using a panel of MAGE-A1 expressing A*01:01-positive cell lines and a xenograft mouse model. Lead TCRs were assessed for potential off-target reactivity using our proprietary SafetyScan platform, which evaluates recognition of antigens from all proteins that comprise the human proteome. Safety was further evaluated by examining alloreactivity to high-frequency Class I HLAs and by testing TCR reactivity to normal primary human cells and cell lines.

Results ReceptorScan identified 1181 TCRs specific for the MAGE-A1 A*01:01 epitope. Following selection of high-expressing and high avidity MAGE-A1-specific TCRs in ActivScan, 14 TCRs were evaluated for their cytotoxic function, and 5 TCRs compared favorably to a clinical-stage benchmark TCR for cytotoxicity and cytokine release. Safety assessment demonstrated that few putative off-target peptides were recognized, minimal alloreactivity was observed to 110 allotypes tested, and no reactivity to target-negative cell lines were observed.

Conclusions A novel HLA-A*01:01 restricted TCR-T cell therapy candidate has advanced to pre-clinical studies. Addition of this product to TScan's ImmunoBank (collection of TCRs) would extend MAGE-A1 TCR-T therapy for solid tumors on three different HLA alleles, potentially expanding the addressable patient population. Importantly, this creates a unique opportunity to simultaneously target tumor antigens presented on HLA alleles on *different* chromosomes, thus circumventing tumor evasion by HLA LOH with the goal of improving patient responses.

Ethics Approval The Testing facility specifically complies with the recommendations of the Guide for Care and Use of Laboratory Animals with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care.

The animal care and use program at Explora, now CR Discovery Services, is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), which assures compliance with accepted standards for the care and use of laboratory animals. IACUC number: EB17–010-301.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0390