**173** EXRESSION OF A MEMBRANE-TETHERED IL-15/IL-15 RECEPTOR FUSION PROTEIN ENHANCES THE PERSISTENCE OF MSLN-TARGETED TRUC-T CELLS

Michelle Fleury, Derrick McCarthy*, Holly Horton, Courtney Anderson, Amy Watt, Adam Zieba, Lindsay Webb, Jian Ding, Robert Tighe, Robert Hofmeister, Dario Gutierrez.
TCR2 Therapeutics, Cambridge, MA, USA

**Background** Adoptive cell therapies have shown great promise in hematological malignancies but have yielded little progress in the context of solid tumors. We have developed T cell receptor fusion construct (TRuC®) T cells, which are equipped with an engineered T cell receptor that utilizes the full complement of TCR signaling subunits and recognizes tumor-associated antigens independent of HLA. In clinical trials, mesothelin (MSLN)-targeting TRuC-T cells (TC-210 or gavocel) have shown unprecedented results in patients suffering from advanced mesothelioma and ovarian cancer. To potentially increase the depth of response, we evaluated strategies that can promote intra-tumoral T cell persistence and function.

**Methods** Primary human T cells were activated and transduced with a lentiviral vector encoding an anti-MSLN binder fused to CD3ε alone or co-expressed with a membrane-tethered IL-15rα/IL-15 fusion protein (IL-15fu). Transduced T cells were expanded for 9 days and characterized for expression of the TRuC, IL-15rα and memory phenotype before subjecting them to in vitro functional assays to evaluate cytotoxicity, cytokine production, and persistence. In vivo efficacy was evaluated in MHC class I/II deficient NSG mice bearing human mesothelioma xenografts.

**Results** In vitro, co-expression of the IL-15fu led to similar cytotoxicity and cytokine production as TC-210, but notably enhanced T-cell expansion and persistence upon repeated stimulation with MSLN+ cell lines. Furthermore, the IL-15fu-enhanced TRuC-T cells sustained a significantly higher TCF-1+ population and retained a stem-like phenotype following activation. Moreover, the IL-15fu-enhanced TRuCs demonstrated robust in vivo expansion and intra-tumoral accumulation as measured by ex vivo analysis of TRuC+ cells in the tumor and blood, with a preferential expansion of CD8+ T cells. Finally, IL-15fu-enhanced TRuC-T cells could be observed in the blood long after the tumors were cleared.

**Conclusions** These pre-clinical studies suggest that the IL-15fu can synergize with TC-210 to increase the potency and durability of response in patients with MSLN+ tumors.

**Ethics Approval** All animal studies were approved by the respective Institutional Animal Care and Use Committees.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.173