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

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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. Among the common ??-chain cytokines, IL-15 uniquely supports the differentiation and maintenance of memory T cell subsets by limiting terminal differentiation and conferring resistance to IL-2 mediated activation-induced cell death (AICD). In the studies described here, we evaluated the potential of IL-15 as an enhancement to TRuC-T cell phenotype, persistence and function against MSLN+ targets.

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.

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