310 Tethered Interleukin-15 (IL-15)/IL-21 to Enhance T Cells for Cellular Therapy

Asset Overview

Product Type	Cell Therapy
Indication	Oncology
Current Stage	Preclinical
Target(MoA)	Co-expressing the tethered IL-15 and IL-21 on T cell membrane
Brief Description	• Synthetic IL-15 and IL-21 molecules for autocrine expression by the engineered therapeutic T cells developed • These molecules were designed with flexible linkers that connect to cell membrane anchors. This, in turn, reduces systemic toxicity caused by free cytokine molecules • Shown that co-expression of the novel IL-15 and IL-21 tethered molecules improves the anti-tumor efficacy of the therapeutic engineered T cells in vivo
Organization	National Institutes of Health

Differentiation

□ **IL-15 and IL-21 to improve ATC therapy**

- Supporting the function of anti-tumor T cells. However, their use in the clinic has been constrained, in part, by dose-limiting toxicity and the need for repeated administration
- T cells that co-express the tethered IL-15 and IL-21 on their cell membrane can increase therapeutic effectiveness of adoptive immunotherapy because it can reduce systemic toxicity caused by free cytokine molecules
- T cells CAR targeting glypican 3 co-expressing IL-15 and IL-21 (Baylor College of Medicine): Phase I (as of 2019 Sep) to evaluate the T cells co- expressing a second generation Glypican 3-specific Chimeric Antigen Receptor with cytokines Interleukin-21 and 15 as immunotherapy for patients with liver cancer
- A phase I clinical trial was conducted to determine safety, adverse event profiles, and the MTD of rhIL-15 in humans (2015). Patients with metastatic melanoma and metastatic renal cancer were infused with different doses of IL-15 (0.3/1.0/3.0 μg/kg/day) for 12 consecutive days and this treatment regimen resulted in markedly altered homeostasis of mainly NK cells, γδ cells, and to somewhat lesser extent of memory CD8+ T cells. Because of clinical toxicity caused by strong cytokine production, the authors stated that rhIL-15 is too difficult to administer intravenously and suggest developing alternative dosing strategies
- Frontiers in Immunology, 2016, Anke Redeker et al. We conclude that although combining ACT with cytokine treatment seems a promising approach, as hold true for treatments that trigger costimulatory pathways, great care must be taken in applying cytokine therapy. The immune effects are not solely confined to the infused T cells and affect many other cells, frequently leading to severe systemic toxicities

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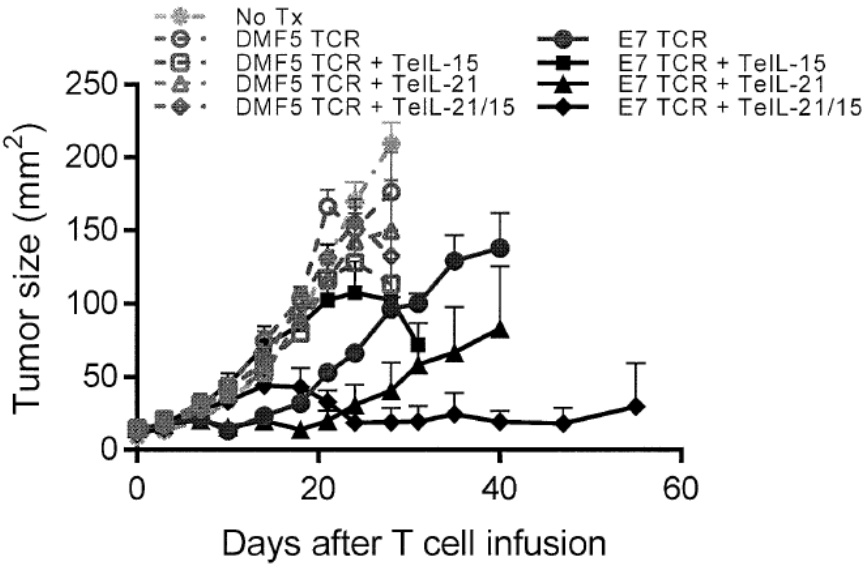
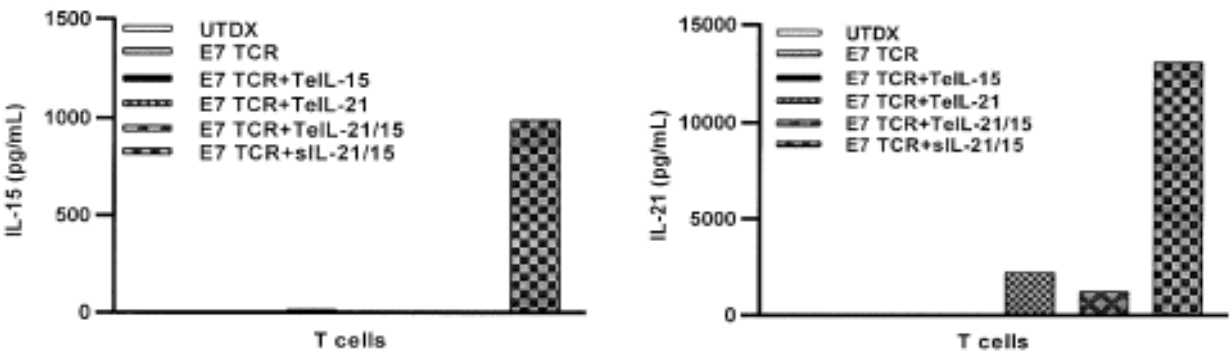
Key Data

In vivo efficacy in CaSki cervical tumor model



- NSG mice were subcutaneously inoculated with 1x10^6 CaSki cervical tumor cells
- CaSki tumor cells: HPV 16 E7 positive & MART-1 negative
- T cells were transduced with an anti-MART-1 TCR (DMF5) alone or the anti-HPV 16 E7 TCR (E7) alone or were co transduced with

Shedding less IL-15 and IL-21 as compared to T cell transduced with secreted IL21/15 *in vitro*



- T cells from a health donor were transduced with (UTDX: untransduced T cells)
- The transduced cells were cultured for 7 days
- T cells were harvested and seeded in fresh media with equal numbers or co-cultured with tumor cells at a one-to-one ratio
- The culture supernatants were collected and proved for IL-15 and IL-21 using the U-PLEAX assay platform

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Intellectual Property

Patent No.	PCT-US2019-016975
Application Date	2019.02.07
Status	Application Pending
Country	

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