Next-Generation, Inducible IL-7–Expressing, Tumor-Infiltrating Lymphocytes by Lentiviral Vector Genetic Modification for Clinical Application

Michael Douglas Crowther,1 Marie Christine Wuff Westergaard,1 Phillip Debnam,2 Victoria Anderson,2 George R. Pope,4 Laura Quinn,3 Emily Schmidt,2 Adel Toth,2 Anoop Chandran2 ZhaoHui Li1, Joseph Sanderson,2 Stine Kier Larsen,1 Marco Donia,1 Ozcan Met,1 Inge Marie Svane1

1National Center for Cancer Immune Therapy (CCIT-DK), Copenhagen University Hospital, Herlev, Denmark; 2Adaptimmune, Abingdon, Oxfordshire, UK

Introduction

- Tumor-infiltrating lymphocytes (TILs) therapy has shown some of the most favorable responses in refractory metastatic melanomas, possibly due to the immunogenicity of this cancer.1
- TILs are isolated from a patient’s own tumor tissue, rapidly expanded in vitro, and then adaptively transferred back into the patient. These TILs can recognize and attack cancer cells in large numbers with high specificity.2
- In multiple Phase I/II trials of melanoma, TIL therapy has demonstrated a robust response rate of up to 50%, however, durable complete responses were only seen in about 15% of treated patients.3
- Immunodeficiency T-cell deficiency is a well-known consequence of T-cell proliferation and survival. However, T-cells are incapable of producing their own IL-7 and rely on secretion from surrounding stromal cells.1
- We hypothesize that the introduction of an inducible IL-7 gene to TILs (next-generation TIL, ADP-TILIL7) will improve their ability to engraft, proliferate, and survive, while maintaining diverse TIL specificity. This may translate into improved clinical activity and durability of response when given to patients.

Development of ADP-TILIL7

- To investigate the ability of IL-7 to enhance T-cell functionality, we first used CD3+ T-cells from healthy donor peripheral blood mononuclear cells with an affinity-enhanced T-cell receptor (TCR) specific for the cancer target antigen melanoma-associated antigen 4 (MAGE-A4) combined with IL-7 under the control of a nuclear factor of activated T-cells (NFAT) inducible promoter in a model system (ADP-A2M4IL7).
- We found that production of inducible IL-7 by ADP-A2M4IL7 led to improved T-cell expansion (Figure 2A). Stimulation of antigen-specific T-cells produced a 6-fold increase relative to total cell number at the start of the assay.
- Young TILs from patient donors were isolated and expanded, followed by activation, IL-7 transduction, and implementation of a rapid expansion protocol (REP; Figure 3A). Transduction of TILs during culture showed a 68% reduction in IL-7 secretion and 92% reduction in vector copy number compared to transducing the TILs before the REP.

Conclusion

- We have developed a reliable transduction method for young TILs utilizing lentivector in the presence of a poloxamer transduction enhancer.
- The ADP-TILIL7 final product produces biologically relevant amounts of IL-7, which has been shown in vitro to maintain survival and prolong proliferation of T-cells.
- Based on our preclinical studies, a single-center, Phase 1 clinical trial will be initiated with ADP-TILIL7 to treat patients with metastatic melanoma.