Positive Combination Effect of ACT and Systemic mWTX-330 Dosing
mWTX-330 Improves the Antitumor Efficacy of pmel+ ATL against B16F10

INDUKINE Molecules Treatment Enhances Effector Functions of ACT
INDUKINE Molecules Therapy Enhances the Polymorphism of pmel+ T Cells in B16F10 Tumors

INDUKINE Molecules Improve the Antitumor Immunity of CAR T Cell Therapy
Systemic INDUKINE Molecule Therapy

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The Combination of ACT and INDUKINE™ Therapy Leads to Improved Antitumor Immunity in Mouse Solid Tumors
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BACKGROUND
Adaptive cell therapy (ACT) utilizes tumor-specific T cells obtained from tumor biopsies or genetically engineered peripheral T cells to treat a patient’s malignancy. Even though there has been clinical success with chimeric antigen receptor (CAR) T cells in hematological malignancies, limited success has been demonstrated with ACT in solid tumors. One of the main limitations of ACT is the high cell number required to treat patients. The cells require repeated in vitro expansion and long-term storage leading to an exhausted, terminally differentiated phenotype, which results in a short-lived antitumor response. This has warranted the need for novel strategies to improve engineering and functionality of cellular therapies against solid tumors.

We have designed IL-2 and IL-12 INDUKINE™ polypeptides (cytokine proto-peptides) modified from peripheral actin via an inactivation domain. They are designed to utilize the unique protease profile of tumors to deliver active cytokines preferentially to the tumor microenvironment. Additionally, our INDUKINE molecules are engineered with a half-life extension domain to improve expression under less frequent dosing. In the following studies, we tested whether our INDUKINE molecules could increase the antitumor and antitumor activity of ACT. Our studies used the pmel transgenic mouse model in which CD8+ T cells express a T cell receptor specific for pmel expressed on melanocytes and melanomas and the human C152 CAR T cell model against subcutaneous Raji tumors.

Key Features of INDUKINE Molecules
- Cytokine release
- IL-2 and IL-12 domains
- Tumor-specific cytokine delivery
- Increased Th1 cytokine production
- Reduced toxicity

Systemic WTX-124 Enhances the Antitumor Activity of ACT
WTX-124 + pmel ACT Improves B16F10 Tumor Control andSurvival

SUMMARY and CONCLUSIONS
- The combination of CAR T cell and systemic IL-2 INDUKINE molecules therapy enhanced antitumor immunity against B16F10 melanoma.
- WTX-124 enhanced tumor engraftment of pmel+ cells in the tumor microenvironment.
- IL-2 enhanced the expression of IFNγ on pmel+ CAR T cells while increasing activation marked by CD38 expression.
- Treatment with both INDUKINE molecules increased the pan cytotoxicity in the tumor microenvironment with WTX-124-based cells to produce IFNγ and Granzyme B, and WTX-124-based/blocks to produce TNF-α and IL-12.
- Systemic WTX-124 administration preferentially expanded CAR T cells whereas WTX-124 expanded CAR T cells.
- CAR T cells engineered to express IL-2 INDUKINE polypeptides have enhanced antitumor immunity against B16F10 tumors and increased survival after cell-engraftment failure.
- Current clinical ACT practices can result in short-term immunity due to heavily differentiated and exhausted T cells in solid tumors. These data demonstrate that the administration of INDUKINE proteins with ACT could reinvigorate CAR T cell function leading to improved engraftment and long-term responses.