Introduction

- Cytokines are potent immunomodulators with great promise for cancer treatment. However, the use of systemic cytokine therapy has been limited due to toxicity and poor pharmacokinetics (PK).
- Interleukin 21 (IL-21) is a pluripotent pro-inflammatory member of the common y-chain family of cytokines.
- IL-21 activates anti-tumor T cell responses, induces B cell activation, and promotes the generation and maintenance of germinal centers and tertiary lymphoid structures.
- IL-21 acts on a broader range of cells than IL-2 and does not induce vascular leak syndrome.
- Clinical use of IL-21 has been hampered by its poor pharmacokinetic properties and adverse events at dose levels associated with efficacy.

WTX-712 is an IL-21 INDUKINE polypeptide containing native human IL-21, an inactivation domain and a half-life extension domain tethered together by protease sensitive linkers.

While WTX-712 is inactive in the periphery, dysregulation of the protease milieu in the tumor microenvironment (TME) results in cleavage of the linkers and the release of IL-21 intracellularly.

WTX-712 contains native human IL-21 as the payload, since human IL-21 has reduced potency on murine cells, we utilized mice expressing the human IL-21 for pre-clinical studies.

Figure 1: Treatment with IL-21 Generates Robust Anti-Tumor Efficacy in Several Synergistic Tumor Models

Figure 2: Differential Efficacy of IL-2 and IL-21 in PD-1 Resistant Synergistic Tumor Model

Figure 3: IL-21 Treatment Activates CD8+ T cells and Drives B cell Class Switching

Figure 4: IL-21 Treatment Drives Transcriptional Changes in TILs of EMT-6 Tumors

Figure 5: WTX-712 is a Selectively Inducible IL-21-Prodrug

Figure 6: Treatment with WTX-712 Results in Robust Anti-Tumor Activity

Figure 7: WTX-712 Reduces Tumor Burden and Activates CD8+ T cells

Figure 8: WTX-712 Improves the Therapeutic Window of IL-21 to Minimize Systemic Toxicities

Conclusions

- Treatment with half-life extended IL-21 demonstrates potent anti-tumor activity in several synergistic tumor models.
- The anti-tumor efficacy driven by IL-21 differs mechanistically from that of another potent common γ cytokine, IL-2, which is also in development for cancer treatment.
- IL-21 promotes the activation and polyfunctionality of CD8+ T cells and drives a favorable CD8:Treg ratio.
- IL-21 treatment leads to transcriptional changes in the TME, with the upregulation of several pro-inflammatory and immuno-stimulatory pathways with the TME.
- WTX-712, an INDUKINE polypeptide containing human IL-21, demonstrates in vitro and in vivo indubitability and activity.
- Systemic administration of WTX-712 drives anti-tumor immune responses resulting in reduced tumor burden and activation of CD8+ T cells in the syngeneic MC38 tumor model.
- WTX-712 has an improved therapeutic window compared to equimolar amounts of half-life extended IL-21.

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