Pharmacologically-controlled expression of membrane-bound IL-12 results in T-cell therapy with enhanced potency in preclinical solid tumor models

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Introduction

Interleukin-12 (IL-12)

IL-12 is a promising candidate for arming cellular therapies such as chimeric antigen receptor T cells (CAR-Ts) or tumor infiltrating lymphocytes (TILs). If its concentration, localization, and toxicities can be controlled:

- Hallmark Th1, proinflammatory cytokine promotes:
  - INFγ and TNFα production
  - T cell and NK cell proliferation and activation
  - Adaptive cell-mediated immunity
  - Repopulates suppressive myeloid cells and tumor associated macrophages (TAMs)
  - Enhances antigen presentation
  - Preclinical efficacy in multiple solid tumor models
- Potential clinical utility limited by toxicity at even moderate systemic concentrations

The Obsidian cytoDRiVE® platform

Obsidian’s cytoDRiVE® platform can be used to control protein expression, acting as a titrable and reversible rheostat for on demand activity

Regulated mbIL-12 enhances anti-tumor efficacy in the syngeneic B16-pmel model and is better tolerated than secreted IL-12

Regulated mbIL-12 reduces and reprograms tumor associated macrophages

Modulation hubs minimize systemic impacts of IL-12 on myeloid cells

Conclusions

Modulation hubs showed greater efficacy than a synthetic solid tumor model, concomitantly normalization modulation hubs mbIL-12 levels are within the linear range for impacting physiologic activities in vivo.

- Localized IL-12 had similar impacts on the tumor microenvironment as secreted IL-12, but fewer systemic effects, suggesting the ability to preferentially deliver the cytokine to a solid tumor and after its mitosis.

Modulation hubs enable regulated efficacy against subcutaneous Raji tumors

Modulation hubs enable regulation of IL-12 in the plasma and on the surface of CAR-T cells leading to regulated control of solid tumor growth at 10x lower cell dose than unarmored CAR-T cells

DRD modulation hubs enable regulated efficacy against subcutaneous Raji tumors

Membrane bound IL-12 has more localized effects and reduced toxicity compared with secreted IL-12

IL-12 regulation and activity in human and mouse cells is controlled by both T-cell activation and ACE

Modulation hubs regulate INFγ in the tumor and plasma, while increasing the localization of cytokine within the tumor microenvironment (TME)

Modulation hubs regulate myeloid cell activation in the blood and the tumor microenvironment

IL-12 reduces and reprograms tumor associated macrophages

In the context of an intact immune system, modulation hubs control systemic and local levels of IL-12 and INFγ with fewer toxic effects than secreted IL-12.

Modulation hubs had similar impacts on the tumor microenvironment as secreted IL-12, but fewer systemic effects, suggesting the ability to preferentially deliver the cytokine to a solid tumor and after its mitosis.