**Abstract**

Activation of costimulatory signals on the tumor microenvironment (TME) is a key target for T-cell mediated antitumor immunity. GITR (glucocorticoid-induced TNFR-related protein) signaling is a key pathway to enhance T cell responses to weakly immunogenic tumor-associated antigens. This pathway is of particular importance in the context of TCR costimulation. GITR signaling in T cells may also provide resilience to the immune suppressive effects of regulatory T cells, thereby enhancing T cell responses to multiple tumor-associated antigens.

**Therapeutic Hypothesis:**

**Paradigm:**

**GITR Functions as a T Cell Costimulatory Molecule**

**INITIAL**

- **GITR Signaling in the Context of TCR Activation Enhances Effector T Cell Activation, Cytokine Production and Cytotoxicity**

**SECONDARY PHASE**

- **GITR Signaling in the Context of TCR Activation Enhances Effector T Cell Activation, Cytokine Production and Cytotoxicity**

**CONCLUSION**

**GITR Signaling in Cancer Immunotherapy**

**The specific hypothesis for this study is that in a TME in locally infiltrating tumor microenvironment and promotes the suppression of regulatory T cell (Treg) function**

**Results**

**INCAGN01876 Binds to Primary Activated T Cells**

**INCAGN01876 Activates γcR1α/IL-21Rα in Activated T Cells**

**INCAGN01876 Enhances Primary T Cell Responses to Suboptimal TCR Stimulation**

**INCAGN01876 Mediates Antibody-Dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells**

**GIRTR is Selectively Expressed by Intratumoral Regulatory T Cells in Multiple Tumor Types**

**Conclusions**

- **INCAGN01876 selectively binds to γcR1α with an affinity of 0.21 nM and binds to activated T cells in a dose-dependent manner.**
- **INCAGN01876 functions as a potent agonist of the GIRTR pathway, and may have the potential to enhance antitumor immunity and to overcome intratumoral Treg cell-mediated suppression.**
- **Samples from various tumor types demonstrate an enrichment in GIRTRhigh intratumoral Treg cells, which is enhanced by TCR costimulation.**

**References**


**Acknowledgements**

The authors would like to thank Rebecca Woelfe for her assistance in preparing poster material and Joseph Connolly and Reid Huber, Peggy Scherle, Gregory Hollis: for their support.

**Employment and Stock Ownership.**

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