MCLA-145 is a bispecific IgG1 antibody that inhibits PD-1/PD-L1 signaling while simultaneously activating CD137 signaling on T cells

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Introduction

- CD137 (O-48) is a transmembrane costimulatory receptor on T and NK cells that enhances adaptive immune responses and is a critical mediator of antitumor immunity.
- CD137 signaling requires receptor clustering by the trimeric CD137 ligand, agonistic monovalent antibodies (mAbs), or antibody cross-linking of CD137 binding antibodies by Fc receptors on neighboring cells.
- PD-L1 expression is frequently observed on tumor cells and in fibroblast-like PD-L1 inhibition has demonstrated durable tumor remission in patients with diverse advanced cancers in the clinic.

MCLA-145 is a CD137/PD-L1 bispecific antibody that releases PD-L1-mediated T-cell inhibition and activates and expands T cells through agoniism of CD137

Unbiased screening of Bioclinics’ library

- A library of >100 CD137 PD-L1 Biclonics® was produced and purified.
- CD137 X PD-L1 Biclonics® were screened in reporter and T-cell activation assays in the absence and presence of PD-L1 expressing CHO cells.
- CD137 X PD-L1 Biclonics® potentially activate T cells in the presence of PD-L1.
- MCLA-145 was selected based on its potency in multiple primary human immune cell assays.

Example of T-Cell Activation Assay Screen on CD137 X PD-L1 Panel (L-2 readout)

MCLA-145 activates T cells and overcomes suppression by M2 macrophages and Tregs

- EC50 of cytokine production was determined in anti-CD3 activated healthy donor T cells (n=7) in the presence of PD-L1 expressing cells.
- Change in cytokine production by anti-CD3/CD28 activated human RNAK upon culturing with human regulatory T cells in the presence of MCLA-145

MCLA-145 blocks ligand binding

- MCLA-145 competes with CD137 ligand binding
- MCLA-145 blocks binding of CD137 to PD-L1 in a face-to-face ligand binding assay
- MCLA-145 blocks PD-L1 binding to PD-L1 in an ELISA-based ligand binding assay
- Analogs are lacking monospecific antibodies

MCLA-145 activity correlates with PD-L1 expression levels

- CD8 T cell lines stably expressing various levels of PD-L1 and human cell lines endogenously expressing PD-L1 were co-cultured with CD137-saturating anti-4B4 reporter cells.
- MCLA-145-mediated CD137 reporter cell signaling intensity correlates with PD-L1 expression levels on neighboring cells

MCLA-145 epitope on CD137

- Domain swap and alanine scanning approaches mapped the MCLA-146 epitope on CD137 to cytosolic N-terminal domain (C-terminal)

MCLA-145 induces CD137 internalization

- MCLA-145 mediates CD137 receptor internalization in human CD8+ T-cells co-cultured with accessory cells expressing PD-L1

MCLA-145 translocates PD-L1 and CD137 to cell contact zone

- CD137-expressing Jurkat T cells and PD-L1-expressing CHO cells cocultured with test antibody were measured for proximity of CD137 molecules (left panel) or PD-L1 and PD-L1 molecule (right panel) by a novel application of Venus (Vg) technology, capable of testing antigen clustering caused by MCLA-145

Conclusions

- MCLA-145 is an Fc-spared Bioclinic® that engages human PD-L1 and CD137 and blocks ligand binding to both receptors.
- MCLA-145-induced CD137 signaling is foreign by PD-L1 and correlates with PD-L1 expression levels.
- MCLA-145 relocates PD-L1 and CD137 to the cell-cell contact zone and clusters CD137 receptors on the T cell membrane.
- MCLA-145 is currently undergoing clinical investigation (NCT03922066)

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