P820

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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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Merus closing in on cancer

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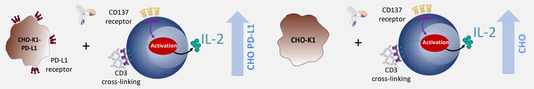
Introduction

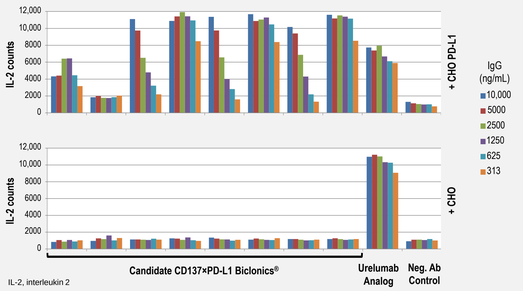
- CD137 (4-1BB) is a transmembrane costimulatory receptor on T and NK cells that enhances adaptive immune responses and is a critical mediator of antitumor immunity
- The development of CD137-targeted agents for cancer therapy has been hampered by on-target off-tumor toxicity
- CD137 signaling requires receptor clustering by the trimeric CD137 ligand, agonistic monoclonal antibodies (mAbs), or indirectly via cross-linking of CD137-binding antibodies by Fcγ receptors on neighboring cells
- PD-L1 expression is frequently observed on tumor cells and mAb-based PD-L1 inhibitors have demonstrated durable tumor remission in patients with diverse advanced cancers in the clinic
- MCLA-145 is a CD137 X PD-L1 bispecific antibody that releases PD-L1 mediated T-cell inhibition and activates and expands T cells through agonism of CD137

Unbiased screening of Biclonics® library

- A library of 192 CD137 X PD-L1 Biclonics® was produced and purified
- CD137 X PD-L1 Biclonics® were screened in reporter and/or T cell transactivation assay in the absence and presence of PD-L1 expressing CHO cells
- CD137 X PD-L1 Biclonics® potently activate T cells in the presence of PD-L1
- MCLA-145 was selected based on its potency in multiple primary human immune cell assays



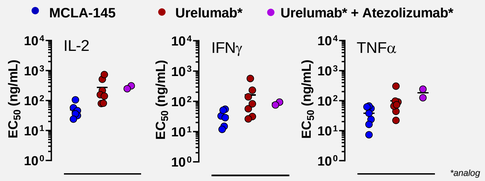
Example of T-Cell Activation Assay Screen on CD137 X PD-L1 Panel (IL-2 readout)



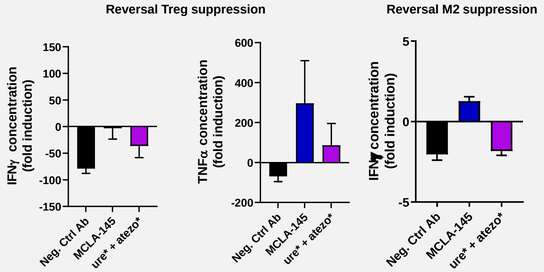
IL-2, interleukin 2

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

- EC_{50} of cytokine production was determined in anti-CD3 activated healthy donor T cells (n=7) in the presence of PD-L1 expressing cells



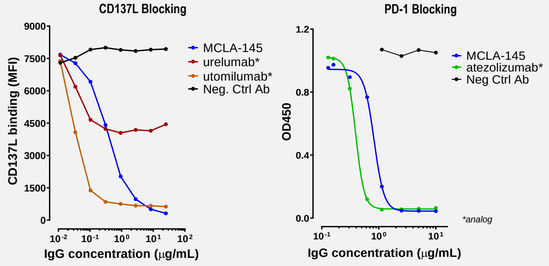
- Change in cytokine production by anti-CD3/CD28 activated human T cells upon culturing with human regulatory T cells or M2-polarized macrophages



*urelumab (ure) and atezolizumab (atezo) analogs

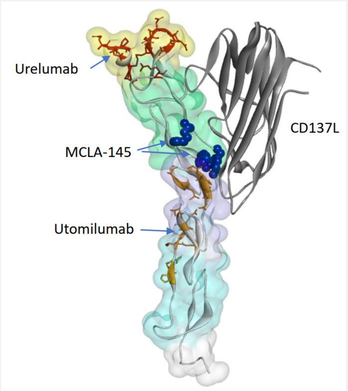
MCLA-145 blocks ligand binding

- All potent CD137 X PD-L1 Biclonics® in the screen, including MCLA-145, compete with CD137 ligand binding
- MCLA-145 blocks binding of CD137L to CD137 in a FACS-based ligand binding assay
- MCLA-145 blocks PD-1 binding to PD-L1 in an ELISA-based ligand binding assay
- Analogs are bivalent antibodies



MCLA-145 epitope on CD137

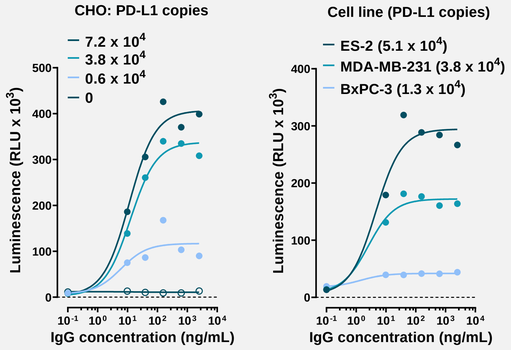
- Domain swap and alanine scanning approaches mapped the MCLA-145 epitope on CD137 to cysteine rich domain (CRD) 2
- Hydrogen/deuterium exchange liquid chromatography mass spectrometry (HDX-MS) confirmed the epitope in CRD2, however, several protected peptides also covered part of CRD3



CRD1 - yellow
CRD2 - cyan
CRD3 - purple
CRD4 - light blue
MCLA-145 critical binding residues - solid blue circles

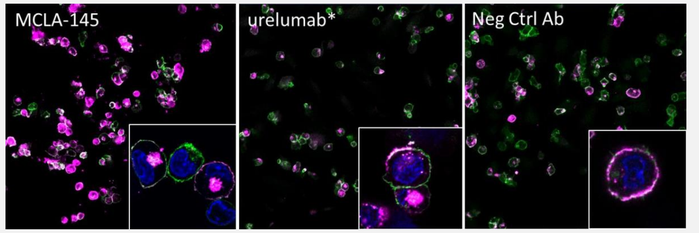
MCLA-145 activity correlates with PD-L1 expression levels

- CHO cell lines stably expressing various levels of human PD-L1 and human cell lines endogenously expressing PD-L1 were co-cultured with CD137 Jurkat NF-kB/luc reporter cells
- MCLA-145-mediated CD137 reporter cell signalling intensity correlates with PD-L1 expression levels on neighbouring cells



MCLA-145 induces CD137 internalization

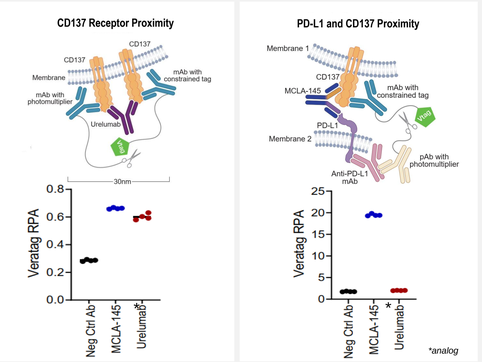
- MCLA-145 mediates CD137 receptor internalization in human CD8+ T cells co-cultured with accessory cells expressing PD-L1



Magenta – CD137, green – CD8, blue – nuclear (DAPI)

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 CD137 and PD-L1 molecules (right panel) by Veratag (Vtag) technology
- Vtag is released if CD137 detection mAbs (left) or CD137 and PD-L1 detection mAbs (right) are within 30 – 100 nm distance
- MCLA-145 and urelumab analog induce clustering of CD137 molecules
- MCLA-145 brings CD137 and PD-L1 within the range of Vtag detection between neighboring cells



Conclusions

- MCLA-145 is an Fc-silenced Biclonic® that engages human PD-L1 and CD137 and blocks ligand binding to both receptors
- MCLA-145-induced CD137 signaling is licensed 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 (NCT03922204)

Disclosures

Liang-Chuan Wang, Jing Zhou, Arpita Mondal, Yao-bin Liu, Thomas Condamine, Alla Volgina, Ashwini Kulkarni, Wilfred Marissen, Cheng-Yen Huang, Leslie Hall, Shane Harvey, Chrysi Kanellopoulou, Shaun Stewart, Horacio Nastri, Patrick Mayes: Employment and stock ownership – *Incyte Corporation;*

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Acknowledgments

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