An Unbiased Screen Identifies a CD137×PD-L1 Bispecific IgG1 Antibody With Unique T-Cell Activation and Binding Properties


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Abstract

CD137 x PD-L1 is a bispecific therapeutic conjugate consisting of a CD137 antibody that enhances T-cell responses and an anti-PD-L1 antibody that blocks PD-L1-mediated T-cell immunosuppression. Here, we report the discovery of a unique CD137 x PD-L1 bispecific antibody, MCLA-145, that stimulates T-cell responses in vitro and in vivo. MCLA-145 is a bivalent CD137×PD-L1 analog with a unique binding profile to CD137 and PD-L1 that is highly efficacious in vitro and in vivo. MCLA-145 demonstrated high affinity and specificity for PD-L1 in a FACS-based bispecific assay and in a competitive ELISA assay. MCLA-145 was highly efficacious in vitro in the induction of T-cell proliferation and IFN-γ production in T-cell lines, as well as in vivo in a humanized mouse model of colorectal cancer. MCLA-145 is a promising therapeutic candidate for the treatment of cancer and other immune disorders.

Antibody Generation

- The mAbs Ab1 to Ab6 were used to generate MCLA-145.
- MCLA-145 is a bispecific antibody consisting of a CD137 and a PD-L1 antibody.
- MCLA-145 was generated using a phage display system.
- MCLA-145 was selected using a FACS-based bispecific assay.
- MCLA-145 was highly efficacious in vitro in the induction of T-cell proliferation and IFN-γ production in T-cell lines.
- MCLA-145 was also highly efficacious in vivo in a humanized mouse model of colorectal cancer.
- MCLA-145 is a promising therapeutic candidate for the treatment of cancer and other immune disorders.

Screening CD137 and PD-L1 Panels

- Large DNA panels were generated for CD137 and PD-L1, and Fab clones were selected for screening.
- Fab clones were screened for affinity, cross-reactivity with cytotoxic T lymphocytes, and murine PD-L1 and CD137 (both divalent and monovalent binding).
- Fab clones with the highest affinity and specificity for PD-L1 were selected for further characterization.
- MCLA-145 blocks PD-L1 within 10 minutes of incubation with PD-L1-expressing cells.
- MCLA-145 is a promising therapeutic candidate for the treatment of cancer and other immune disorders.

MCLA-145 Blocks Ligand Binding

- Binding epitopes were identified using CD137 immunopeptide microarrays and a high-throughput screening assay.
- MCLA-145 blocks the ligand-binding domain of CD137.
- MCLA-145 is a promising therapeutic candidate for the treatment of cancer and other immune disorders.

Conclusions

- MCLA-145 is an Fc-replacement bispecific that engages requisite CD137 and PD-L1 and blocks ligand binding in both receptors.
- MCLA-145 blocks ligand binding and is present in its epitopes.
- The unique binding properties of MCLA-145 may result in an increased therapeutic window by specifically activating CD137+ T cells in the tumor microenvironment where PD-L1 is expressed, while simultaneously blocking checkpoint inhibition on CD8+ T cells.

Disclosures

- Hummingbird Biologics, Yin Huang, Jing Zhou, Shaun Stewart, Cheng-Yen Huang, Patrick Mayes, Gregory Hollis, Reid Huber, Mark Throoby.
- Merus Netherlands B.V., Utrecht, Netherlands.
- University Medical Center, Utrecht, Netherlands.
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Image

Screening CD137+PD-L1 Biclonics® Library

- Example of T-cell Activation Assay (CD137+PD-L1 Panel, 2-readout).
- MCLA-145 blocks PD-L1 within 10 minutes of incubation with PD-L1-expressing cells.
- MCLA-145 is a promising therapeutic candidate for the treatment of cancer and other immune disorders.