DISCOVERY OF MACO-355, A NOVEL, FIRST IN MECHANISM LIGAND-BLOCKING INDEPENDENT ANTI-LILRB1/2 MONOCLONAL ANTIBODY FOR CANCER THERAPY

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Background Macrophages populate most solid tumors in large numbers and limit effective anti-tumoral immune responses. The immunoreceptor tyrosine-based inhibitory motifs (‘ITIMs’) containing leukocyte immunoglobulin-like receptors (LILR) B1 and LILRB2 are expressed on tumour associated macrophages. Despite sharing multiple ligands such as major histocompatibility complex class I G (HLA-G), LILRB1 regulates phagocytosis, whereas blocking of LILRB2 ligand binding was shown to enhance cytokine release. To date, therapeutic approaches to targeting LILRB1 and LILRB2 have blocked receptor – ligand interaction to relieve ligand-mediated immune suppression. To obtain antibodies with novel and possibly superior LILRB1/LILRB2 modulating activity we investigated both ligand blocking and non ligand-blocking clones.

Methods Fully human antibodies were identified via immunization of mice with the full length ectodomain of LILRB1 but were screened for LILRB2-mediated reprogramming effects to identify dual LILRB1 and LILRB2 targeting antibodies. Antibodies were assessed for LILR family member binding, ligand neutralization, and functional activity in a range of macrophage cell assays including T cell suppression and tumour cell cocultures. Reprogramming was tested under immune suppressive conditions (such as colony-stimulating factor (CSF) 1, transforming growth factor beta (TGFβ), interleukin (IL) 10).

Results We have identified MACO-355, a novel, dual LILRB1 and LILRB2 targeting antibody that does not block ligand binding capable of mediating macrophage reprogramming under strong immune suppressive conditions. MACO-355 was selected from the pool of LILRB1 and LILRB2 binders with the most potent macrophage reprogramming activity. Surprisingly, these antibodies do not neutralize ligand (HLA-G, HLA-A, HLA-E) binding to LILRB1/2. Nevertheless, they induce macrophage phagocytosis irrespectively of tumour ligand expression status and retain NK and T cell activation via LILRB1. Notably, MACO-355 was unique amongst identified macrophage reprogramming antibodies in being able to stimulate pro-inflammatory cytokine production by immune suppressed macrophages such as IL10 and TGFβ treated or cancer cell coculture. Concordantly, stimulation of cells with MACO-355 also resulted in significantly higher levels of T cell expansion, proliferation, and interferon gamma release in a macrophage/T cell coculture suppression assay. Molecular studies showed MACO-355 binds a novel epitope in domain D3-D4 on LILRB1/2 resulting in pronounced modulation of intracellular kinase signaling.

Conclusions MACO-355 is a first in mechanism ligand-blocking independent LILRB1/2 antibody and is highly potent in macrophage reprogramming under tumour-like immune suppressed conditions. These data support the future clinical evaluation of MACO-355 as a cancer therapeutic.

REFERENCES

Ethics Approval The use of human material in this study (IRAS project ID: 311780) was approved by the East Midlands – Derby Research Ethics Committee.

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