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


1Macomics, Cambridge, UK; 2Macomics, Edinburgh, UK

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 tumor 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 (TGFb), 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 TGFb 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.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0518