animal models, knockdown of GM-CSF in pancreatic epithelium or pancreatic mesenchymal stem cells inhibits tumorigenesis, reduces intra-tumor MDSCs and enhances CD8+ T cell accumulation. Therefore, targeting the GM-CSF receptor alpha (GM-CSFRα) on MDSCs is an attractive strategy to restore anti-tumor immunity. Mavrilimumab is a clinical stage human monoclonal antibody that blocks GM-CSFRα. It has demonstrated efficacy and acceptable safety profile in patients with rheumatoid arthritis, and it’s currently undergoing investigation in phase II studies in giant cell arteritis and in patients with severe COVID-19 pneumonia and hyper-inflammation (NCT03827018, NCT04397947, respectively). The present study investigates its potential as a therapeutic strategy to target MDSCs in the TME as an adjuvant to immunotherapy.

Methods Cancer cell supernatants were collected when cells reached confluence. Human GM-CSF was measured by ELISA. Healthy donor CD14+ monocytes were incubated with cancer cell supernatants for either 3 or 6 days followed by phenotypic analysis (CD14, CD3, HLA-DR, CD11b, CD206, CD80, PD-L1, Arginase-1) by flow cytometry. On day 3, autologous CD3+ T cells were stimulated with CD3/CD28 and IL-2 and co-cultured with putative MDSCs for 5 days. T-cell proliferation was evaluated by measuring carboxyfluorescein succinimidyl ester (CFSE) dilution in CD4+ and CD8+ T cells by flow cytometry.

Results GM-CSF is expressed in the supernatant of cancer cell lines (HCT116, SW-480, Panc-1, Capan-1). Human monocytes cultured with conditioned medium from colorectal carcinoma (SW-480) or pancreatic adenocarcinoma (Capan-1) show downregulation of HLA-DR, increased expression of PD-L1, Arg-1, CD206, and can suppress T-cell proliferation in vitro. Similarly, peripheral blood monocytes purified from pancreatic cancer patients suppress T-cell proliferation ex vivo. Notably, Mavrilimumab inhibits the polarization of healthy donor monocytes to M-MDSCs and restores T-cell proliferation.

Conclusions Targeting of GM-CSFRα with mavrilimumab may alleviate the pro-tumorigenic and immunosuppressive functions of MDSCs in the TME. Future clinical studies should evaluate whether targeting of the GM-CSFRα in combination with immune checkpoint inhibitors is a viable therapeutic option to bolster their efficacy.

Ethics Approval The study was approved by the Institute of Immunology and Immunotherapy, University of Birmingham, UK Ethics Board. Healthy volunteer human material was obtained from commercial sources and approved by Stemexpress Institutional Review Board (IRB).

REFERENCES