1356 DM926, A NOVEL ANTI-LILRB1/LILRB2 DUAL ANTAGONIST ANTIBODY, PROMOTES ADAPTIVE AND INNATE IMMUNE RESPONSE TO ENHANCE ANTI-TUMOR ACTIVITY IN PRECLINICAL MODELS

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Background Genome-wide association studies (GWAS) have identified HLA-G and LILRB1/2 loci associated with cancer risk. LILRB1 and LILRB2 are distinct inhibitory immune checkpoint receptors. LILRB1-mediated inhibition leads to impairment of cytotoxicity and proliferation of T cells and preventing the efficient engulfment of tumor cells by macrophages as a 'don't eat me' signal. LILRB2 suppresses the stimulation immune response of myeloid cells, especially in the tumor microenvironment. Blocking LILRB1/LILRB2 interaction with their ligands can be an effective immunotherapy for treating cancer. D2M has developed a dual antagonist antibody targeting both LILRB1 and LILRB2, named DM926.

Methods DM926 was characterized in a series of assays to evaluate biological and physicochemical properties. DM926 was assessed in a series of *in vitro* functional assays using human PBMC, CD8+ T cells, NK cells, human monocyte-derived macrophages (hMDMs), tumor-associated macrophages (TAMs) and Dendric cells (DC). The target occupancy was performed in human whole blood *in vitro* and in LILRB1/2 transgenic mice *in vivo*. The stability was evaluated *in vitro* in fresh human serum and *in vivo* in B6 mice and LILRB1/2 transgenic mice. DM926 was evaluated in multiple xenograft mouse tumor models with adoptive transfer of human macrophages or PBMC.

Results DM926 has sub-nanomole binding affinities to both LILRB1 and LILRB2. DM926 efficiently blocked the interactions of LILRB1 and LILRB2 to their ligands. DM926-mediated LILRB1/2 blockade modulated the function of immune cells: 1) released HLA-G mediated inhibition on TCR activation in Jurkat cells over-expressing LILRB1; 2) enhanced the cytotoxicity of CD8+ T cells and NK cells to lyse tumor cells; 3) enhanced phagocytosis of tumor cells by macrophages; 4) enhanced TNFα expression and inhibited IL10 expression in LPS-stimulated human PBMC; 5) reprogramed both hMDMs and TAMs induced by tumor cells to polarize toward a more inflammatory phenotype, leading to enhanced T-cell responses stimulated by DCs and inhibition of tumor cell growth. DM926 exhibited efficient target occupancy and stability *in vitro* and *in vivo*. DM926 demonstrated significant anti-tumor activity in xenograft tumor models with adoptive transfer hMDM or PBMC.

Conclusions DM926 has demonstrated desirable characteristics. DM926 reprograms suppressive myeloid cells to a stimulatory state, eliciting phagocytotic function of macrophages, promoting cytotoxicity of CD8+ T and NK cells, and enhancing the activation of lymphoid cells. DM926 demonstrated significant antitumor activities in mouse tumor models. DM926 exhibited excellent stability *in vitro* and *in vivo*. The data warranted further development of DM926 as an immunotherapeutic for solid malignancies.

Ethics Approval All uses of human material have been approved by the Institutional Review Board at ABI-Lab. All animal studies and procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at Worcester Polytechnic Institution (WPI).

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