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) reprogrammed 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 of human macrophages or PBMC.

Conclusions DM926 has demonstrated desirable characteristics. DM926 reprograms suppressive myeloid cells to a stimulatory state, eliciting phagocytic 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).