Preclinical Evaluation of JTX-8064, an Anti-LILRB2 Antagonist Antibody, for Reprogramming Tumor-Associated Macrophages

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ABSTRACT

Introduction: Jounce has generated cell type-specific gene signatures as a means of probing the Cancer Genome Atlas and other large datasets to identify targets that may be important immune checkpoints. Using a human-associated macrophage (TAM) gene signature, we have found a strong correlation and coherence between TAMs and LILRB2 negative immunophenotypic like receptor B2, a T2-like macrophage across multiple tumor types. LILRB2 is a myeloid cell surface receptor containing four extracellular immunoregulation domains, a transmembrane domain, and three cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Ligation of LILRB2 is reported to lead to the activation of both a negative and more inflammatory phenotype - secreting higher levels of TNF-α and IL-6 with decreased amounts of IL-10 and TGFβ as compared to an immune control antibody. Notably, this effect is dependent on the presence of LRRB2 activating receptors. A number of activating receptors (LILRA) have been identified, but the receptor specificity that leads to this phenotype is not well understood. Here we describe 1 a comprehensive evaluation of JTX-8064, a humanized antibody against LILRB2, in syngeneic mouse models to further elucidate the role of LILRB2 in macrophage function.

Methods and Results: JTX-8064 is a humanized LILRB2 neutralizing mAb that inhibits LILRB2 signaling. In vitro, LILRB2 is expressed on human monocyte-derived macrophages and binds HLA-G. In vivo, JTX-8064 potently blocks HLA-G and HLA-A2 tetramers from binding to human monocyte-derived macrophages using on-cell binding assays (Figure 5).

Results: LILRB2 expression is highest on macrophages within the tumor microenvironment. JTX-8064 potently blocks HLA-G and HLA-A2 tetramers from binding to human monocyte-derived macrophages using on-cell binding assays (Figure 5).

Conclusions: JTX-8064 block LILRB2 in a cell type-specific manner to induce a shift in macrophage polarization towards an M1-like state, characterized by increased pro-inflammatory cytokine production and decreased M2-like cytokine production. JTX-8064 is a novel immune checkpoint inhibitor that selectively targets macrophages and has the potential to enhance anti-tumor immunity by reprogramming tumor-associated macrophages.