ANTIBODY BLOCKADE OF THE IMMUNOINHIBITORY RECEPTOR SIGLEC 10 POLARIZES TUMOR ASSOCIATED MYELOID CELLS AND PROMOTES ANTI-TUMOR IMMUNITY

1Julia Schanin*, 1Thuy Luu, 1Robert Sanchez, 1Milene Peterson, 1Lisa McEwan, 2Evan Henneberry, 1Katherine Chang, 1Wouter Korver, 1John Leung, 1Bradford Youngblood.
1Allakos Inc, San Carlos, CA, USA; 2LM Biostat Consulting Inc., British Columbia, Canada

Background Myeloid cells are the most abundant immune cells within the tumor microenvironment (TME) where they play important roles regulating anti-tumor immunity. Targeting myeloid-specific inhibitory receptors to modulate the TME represents an attractive strategy to improve the therapeutic outcome of current cancer immune therapies. Siglec-10 is an inhibitory receptor expressed on tumor-associated macrophages (TAMs) and dendritic cells that regulates immune cell activation via immunoreceptor tyrosine-based inhibitory motifs. Recently, Siglec-10 was induced to induce immunosuppression and promote tumor immune escape through interaction with CD24. Similarly, CD52 and vascular adhesion protein-1 have been shown to drive immunosuppression via Siglec-10, indicating that Siglec-10 functions as an inhibitory receptor through multiple ligands. Here, we report that Siglec-10 expression is upregulated in human tumors and blockade of Siglec-10 with a monoclonal antibody (mAb) enhances proinflammatory responses and delays tumor growth in vivo by modulating myeloid cell function.

Methods Siglec-10 expression was evaluated in human tumors by flow cytometry and RNA-sequencing. Anti-human Siglec-10 mAbs were generated using hybridoma technology and recombinantly produced on mouse IgG1 backbones. Internalization and function of Siglec-10 mAbs were evaluated in vitro by flow cytometry and cytokine production using isolated human CD16+ monocytes. To assess the in vivo activity of a Siglec-10 mAb, transgenic mice expressing Siglec-10 were generated and challenged with poly I:C. Anti-tumor activity of a Siglec-10 mAb was determined using the MC38 syngeneic mouse model.

Results RNA-sequencing data revealed high expression of Siglec-10 across multiple tumors compared to normal tissues, including glioblastoma, colorectal carcinoma, and kidney renal clear cell carcinoma. Specifically, Siglec-10 was found to be highly and selectively expressed on intratumor dendritic cells and macrophages. Siglec-10 mAb treatment blocked ligand binding, induced complete receptor internalization, and significantly enhanced TLR-mediated human monocyte activation in vitro. Similarly, in vivo administration of a Siglec-10 mAb induced receptor internalization and enhanced TLR-mediated inflammation as evidenced by increased levels of cytokines, such as TNF and IL-12p40 (figure 1). To assess the potential of a Siglec-10 mAb as an anti-cancer immunotherapy, we established a colon carcinoma model in Siglec-10 transgenic mice. Siglec-10 mAb blockade polarized myeloid cells towards an inflammatory phenotype, enhanced adaptive immune cell activation and promoted anti-tumor activity.

Conclusions Siglec-10 is highly expressed on tumor-associated myeloid cells and antibody blockade promotes anti-tumor immunity through activation of TAMs and dendritic cells. Our findings highlight Siglec-10 as a promising myeloid cell target for enhancing anti-tumor immunity in solid tumors.

Ethics Approval All legal and ethical requirements have been met with regards to the humane treatment of animals described in this study.