485 FUNCTIONAL CHARACTERIZATION OF THE INHIBITORY ACTIVITY AND IDENTIFICATION OF NOVEL T-CELL RECEPTORS FOR THE TUMOR-ASSOCIATED MACROPHAGE RECEPTOR VSIG4

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[1]Tim Eitas*, [1]Edward van der Horst, [1]Faith Finley, [1]Thomas Thisted, [1]Kanam Malhotra, [1]Arnab Mukherjee, [1]Zuzana Biesova, [1]Anokhi Cifuentes, [2]Sandra Marder, [2]Paul Helbling, [1]Robert Pierce. *[1]Sensei Biotherapeutics, Boston, MA, United States; [2]Dualsystems Biotech AG, Schieren, Switzerland*

Background Tumor associated macrophages (TAMs) are important regulators of immunosuppression in the tumor microenvironment (TME) and are often associated with poor clinical responses in patients. VSIG4 (V-Set and Immunoglobulin domain containing 4) is a negative checkpoint regulator (NCR) and its expression has been well established on both tissue resident macrophages and TAM populations.[1-3] However, the inhibitory molecular mechanism of VSIG4 remains largely unknown[1 2] and many therapeutic strategies targeting TAMs in general have been limited either by a lack of TME-specificity or high target abundance leading to target-mediated drug disposition (TMDD).[4 5] The development of immunomodulatory antibodies that selectively target antigens in acidic environments, such as the TME, has the potential to increase tumor exposure and reduce toxicity.[6]

We have characterized endogenous expression patterns of VSIG4 and observed an absence of expression on peripheral immune cell populations but a significant induction on differentiated primary macrophages under conditions similar to the TME. Additionally, we have performed a proteomics screen for potentially novel T-cell receptor(s) that interact with VSIG4.

Methods Endogenous expression patterns of VSIG4 were characterized in primary human immune cell populations including whole blood, peripheral blood mononuclear cells (PBMCs), and polarized macrophage populations. The induction of VSIG4 expression in polarized macrophage populations was demonstrated by both flow cytometry and RNA expression analysis. A Ligand Receptor Capture-Trifunctional Chemoproteomic Reagents (LRC-TriCEPS)-based proteomics strategy was used to identify receptors on primary human T-cells that interact with recombinant VSIG4 protein.[7]

Results Our results show a robust upregulation of VSIG4 expression in polarized human macrophage populations. Additionally, we established multiple functional assays demonstrating VSIG4-mediated suppression of primary human T-cells. Finally, the LRC-TriCEPS-based proteomics screen yielded novel candidate receptors that interact with VSIG4.

Conclusions VSIG4 inhibits human T-cell activation in multiple assay formats and through numerous functional measurements. A group of T-cell receptors was found to be involved in novel interactions with VSIG4, and their potential roles in VSIG4-mediated regulation are currently being validated. Collectively, our work will lead to an enhanced mechanistic understanding of how VSIG4 suppresses T-cell activation and provide a strategy and tools for discovery of therapeutic relevant anti-VSIG4 antibodies.

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