Novel targeting of tumor infiltrating myeloid derived suppressor cells (MDSCs) through expression of the tumor-specific glycan antigen Sialyl Tn (STn)

David A Eavarone1, Patricia E Rao2, Jillian Prendergast3, Adam D. Curtis2, Lindsay S. Shopland2, Jenna Stein1, Jeff Behrens1 and Daniel T Dransfield1

Affiliations: 1Siamab Therapeutics (Newton, MA), 2Eastern Maine Medical Center (Bangor, Maine)

STn is a Novel Targeting Agent on Myeloid Derived Suppressor Cells

Humanized anti-STn ADCs inhibit tumor growth in cell line and patient derived ovarian carcinoma xenograft models

Abstract

STn, the sialylated version of the carbohydrate Tn antigen, is rarely expressed in normal adult human tissues however it frequently occurs in human cancers such as breast, ovarian, bladder, cervical, colon, and lung cancer demonstrating high tumor specificity and broad tumor expression. Furthermore, the presence of STn in tumors is associated with metastatic disease, poor prognosis, and reduced overall survival.1 We have generated anti-STn mAbs having no cross-reactivity to the asialylated form of STn (Tn) or other glycan antigens.2 The epitope targeted by these mAbs is the STn glycan itself, not a particular glycoprotein or carrier protein, which offers the broadest potential to bind to multiple glycoprotein or glycolipid antigens on tumor cell surfaces. We have used these mAbs to measure quantitatively the expression of tumor STn across a set of patient samples and for the first time demonstrated the expression of tumor STn across subsets of infiltrating myeloid derived suppressor cells (MDSCs). MDSCs are major regulators of immune responses in cancer and other pathological conditions. MDSCs are functionally defined by their capacity to suppress T cell immunity; therefore inhibiting these cells is of great interest for immuno-oncology applications. We have further evaluated the correlation between STn expression and tumor STn expression using murine xenograft models of tumors with controlled STn expression. Using anti-STn antibody-drug conjugates (ADCs), we have demonstrated that STn provides a uniquely glycan-specific and potent targeting mechanism for treatment of solid tumors. STn expression on MDSCs offers the potential to go beyond tumor targeting with an anti-STn therapeutic to also directly target and deplete immune-suppressive MDSCs, fostering immune re-engagement and possibly better patient outcomes. The emerging understanding of glycans in immunity and specifically MDSC biology suggests the potential for a functional role of STn as well and provides a compelling opportunity to directly impact MDSC function with immuno-therapeutic applications.

STn (A) Growth curve in treated athymic nu/nu mice of OVCAR3 (isotype ADC: red; ST1: black). (B) STn+ Tumor MDSCs + ST1. (C) Spleen MDSCs subpopulations. (D) STn+ MDSC depletion in the spleen at the conclusion of the study following STN treatment (mMDSC ST1 (red); PMN-MDSC ISO (left); PMN-MDSC ST1 (right)).

Conclusions and Future Directions

1. STn is differentially expressed across primary patient tumors and we have demonstrated for the first time that STn is also expressed on tumor MDSCs.

2. MDSC STn expression may be dependent upon tumor STn expression as evaluated in a forced STn expression MDA-MB-231 xenograft model.

3. Anti-STn-MM4 ADCs do not directly deplete tumor MDSCs but may however have some effect on spleen MDSCs through ADC. More suitable antibody-drug conjugates for direct MDSC killing are being evaluated.

Contact: David@Siamab.com

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90 Bridge Street Suite 100, Newton, MA 02458

Literature Cited