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DISCOVERY OF HIO 3 A TUMOR-PRODUCED PROTEIN THAT BINDS THE HUMAN IGG1 FC CH3 DOMAIN AND SUPPRESSES ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY AND COMPLEMENT DEPENDENT CYTOTOXICITYNicolas Nicolaides, Luigi Grasso, Brad Kline*. *Navrogen Inc., Cheyney, PA, USA*

Background Human cancers employ a number of mechanisms to evade host immune responses against novel antigens generated from aberrant over-expression, mutations and/or epigenetic alterations. Humoral immunity utilizes antibodies and immune-effector cells as well as molecular immune complexes involving the complement system to mediate the killing of dysregulated cancer cells. We refer to these anti-cancer mechanisms as Humoral Immuno-Oncology (HIO). Suppression of HIO is mediated by tumor-produced proteins called HIO factors. One such factor is CA125, which was previously shown to bind IgG-type antibodies and inhibit their antibody dependent (ADCC) and complement dependent (CDC) cellular cytotoxic activities. Using a combination of experimental screening and literature searches, we screened a number of proteins that have been produced by tumors and associated with a variety of cancer indications to determine if they could impact HIO. Herein, we describe the initial characterization of soluble ICAM-1 (sICAM-1), a tumor antigen capable of binding IgG-type antibodies that inhibits their immune-effector activity.

Methods Deletion and site-directed mutagenesis of the heavy constant domain of IgG1 was performed and constructs expressed as GST fusions in 293F cells. Recombinant proteins were then used in direct binding and competition ELISA formats to determine amino acid residues essential for binding of HIO-3. Constant region mutants that lost HIO-3 binding were then generated to whole IgG constructs for in vitro characterization of HIO-3 resistance.

Results Amino acid substitutions in this domain were able to abrogate sICAM-1 binding and overcome ADCC suppression.

Conclusions These findings highlight yet another mechanism by which tumors can suppress the host's immune system for survival and offers new concepts for developing antibody-based therapies that can aid in the treatment of various cancer indications. Moreover, the findings here offer clinical design opportunities to improve upon existing approved immune-mediated therapies for which this factor is present.

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