Abstract 2356 NAV-006 - A next-generation rituximab targeting CD20 for the treatment of B-cell lymphomas immunosuppressed by CA125

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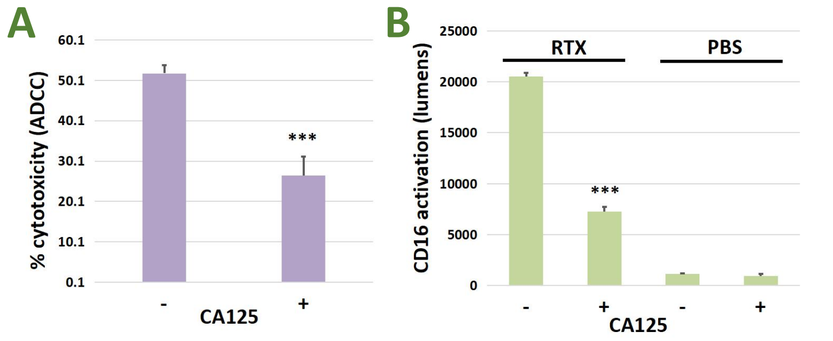
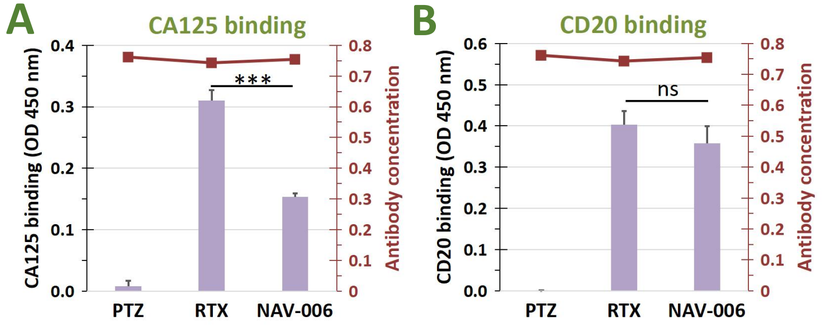
CD20-targeting rituximab (RTX) is the standard-of-care for non-Hodgkin's lymphoma (NHL) patients. Its mechanism of action includes complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). Recent clinical evidence suggests that high serum levels of the tumor-produced MUC16 protein (a.k.a. CA125) has a negative impact on the effectiveness of rituximab clinical activity on up to 40% of follicular lymphoma patients. We have demonstrated that CA125 binds to rituximab and reduces its tumor cell killing activity (fig. 1) and generated a rituximab variant, named NAV-006, using a proprietary technology called Block-Removed Immunoglobulin Technology (BRITE). NAV-006 is refractory to the immunosuppressive effects mediated by CA125 via its reduced CA125 interaction (fig. 2) and increased CDC and ADCC activity versus parent RTX (fig. 3). We also show that other CD20-targeting mono- and bispecific antibodies clinically approved or being tested in relapsed/refractory disease are inhibited by CA125 (fig 4). Finally, we demonstrate NAV-006's efficacy and its superior activity over rituximab *in vivo* by using an animal model of human NHL (fig. 5). These data warrant further investigation of NAV-006 as a next-gen anti-CD20 with improved efficacy in NHL patients with high levels of MUC16/CA125.

Fig. 1 - CA125 inhibits rituximab activity



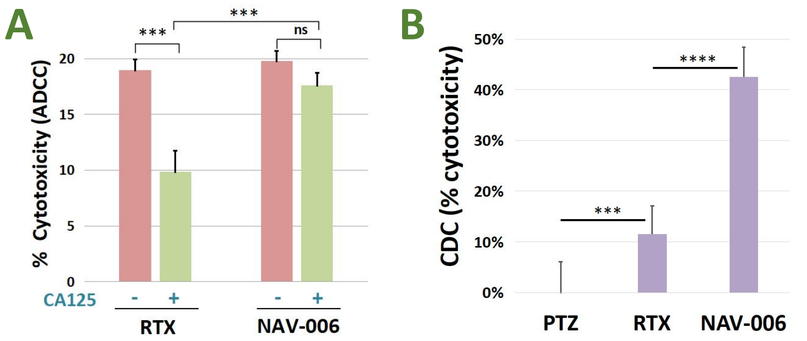
CA125 inhibits RTX-mediated ADCC and Fc receptor/CD16a activation. A) CD20-positive Daudi cells were targeted with RTX (30 μg/mL) + human PBMCs (effector/target ratio of 10:1). CA125 (50,000 U/mL) was added in some cultures and showed to be immunosuppressive against RTX-mediated ADCC compared to cultures without CA125. B) CD16a activation mediated by RTX was significantly inhibited by CA125.

Fig. 2 - NAV-006 / CA125 reduced binding



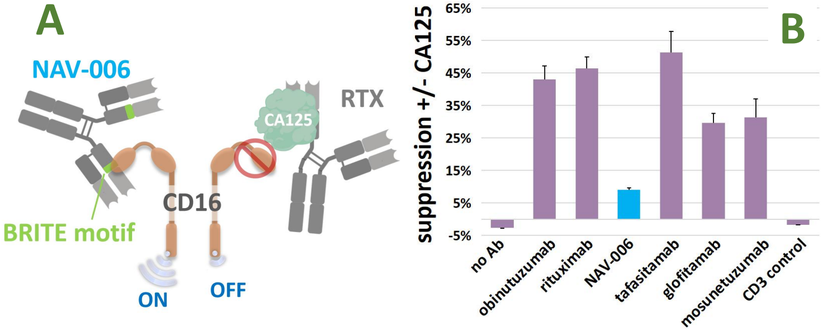
A) Antibody binding to CA125 was measured by using an ELISA. Binding of NAV-006 to CA125 was found to be reduced by >50% compared to RTX and the difference was statistically significant ($p<0.00009$).
B) Antibody binding to CD20 was measured by using an ELISA. NAV-006 CD20 binding was comparable to RTX and the difference was not statistically significant ($p>0.21$).

Fig. 3 - NAV-006 has enhanced ADCC & CDC



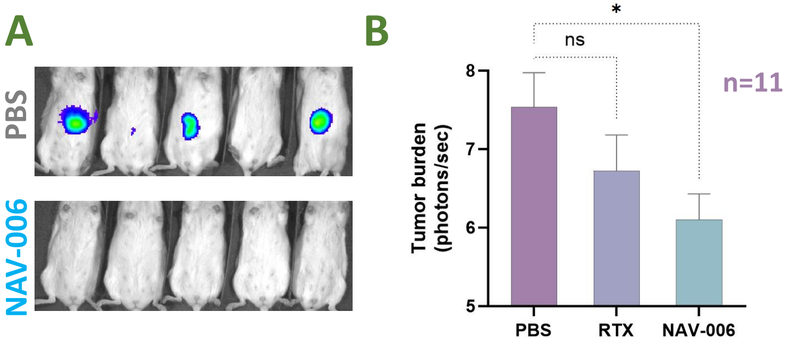
A) Human PBMCs-mediated killing of Daudi cells (effector:target ratio 5:1), +/- CA125 (25 KU/mL). NAV-006 mediated ADCC in the presence of CA125 is significantly higher than parent RTX. B) CD20-positive cells expressing CA125 were targeted with antibodies in the presence of complement. NAV-006 shows superior CDC activity compared to parent RTX. ***$p<0.001$ and ****$p<0.0001$. ns, non-significant. PTZ, pertuzumab.

Fig. 4 - CA125 suppresses other Ab-based NHL drugs



A) Schematic of NAV-006's MoA: the BRITE motif engineered in NAV-006 allows it to escape CA125 blockade and activate CD16/Fc receptors to elicit humoral immunity (ADCC/CDC). B) Monospecific and bispecific antibodies currently approved or being clinically tested in the NHL setting showed reduced ADCC activity in the presence of CA125 compared to NAV-006.

Fig. 5 - NAV-006 vs. RTX in a NHL mouse model



NAV-006 shows superior anti-tumor effect vs. RTX in a lymphoma model *in vivo*. A) Representative ventral images of mice showing tumor burden: Bioluminescent human lymphoma Raji cells were implanted i.p. into Charles River NCG mice and treated with PBS or 1 mg/kg single-dose of either RTX or NAV-006. B) Tumor burden measured on day 28 by bioluminescent imaging. One-way ANOVA + Dunnett multiple comparison.