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NAV-003 A Full-Length IgG Bispecific Targeting Mesothelin With Improved Cytotoxicity Against Humoral Immunosuppressed Tumors

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Leaders in Humoral Immuno-Oncology

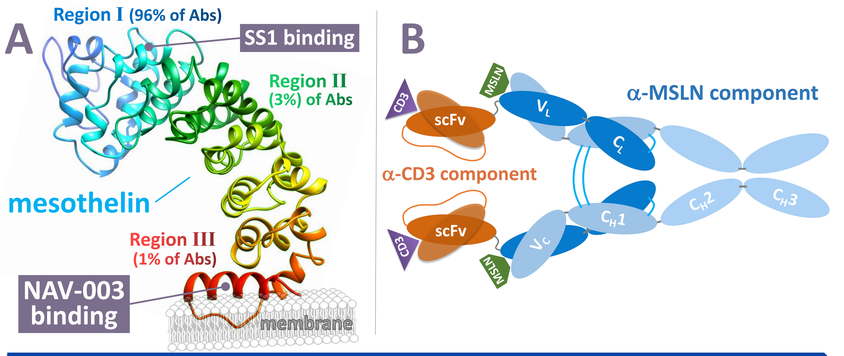
Mesothelin (MSLN) is a validated target – Various antibodies, ADCs and CAR-T therapies targeting MSLN are being tested in clinical trials.

New bispecifics are needed for maximal performance – Studies on antibody and CAR-T agents have shown the importance of particular MSLN epitopes for optimal activity. Also, certain MSLN$^+$ tumors produce proteins that bind to subsets of therapeutic IgG1s, thus suppressing their cytotoxic activities mediated via their Fc domains.

NAV-003 has an optimized configuration – Humanized, full-length, divalent α-MSLN/α-CD3ε bispecific IgG that 1) has extended serum half-life, 2) avoids suppressive factors, 3) targets a MSLN epitope proximal to the cell membrane, and 4) effectively binds, activates and redirects T-cells to the surface of MSLN-positive tumor cells.

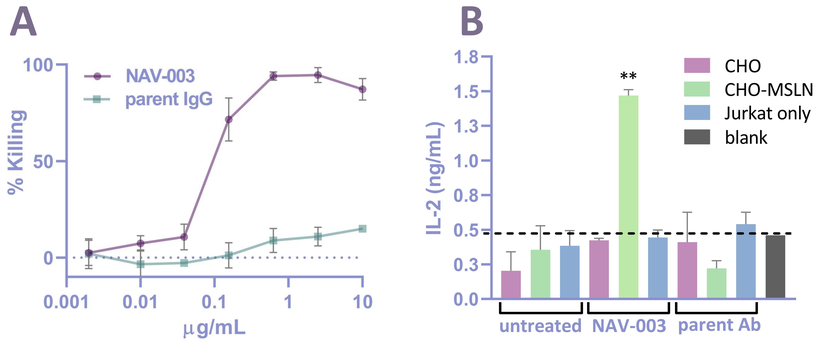
NAV-003 elicits anti-tumor responses in PDX models – NAV-003 is active *in vitro* and *in vivo* even when the Fc domain function is removed and specifically kills MSLN$^+$ tumors via CD3-redirected T-cell mediated cytotoxicity. In a patient-derived MSLN$^+$ and CA125$^+$ mesothelioma model, NAV-003 elicits significant anti-tumor responses.

Fig. 1 - NAV-003's unique epitope & configuration



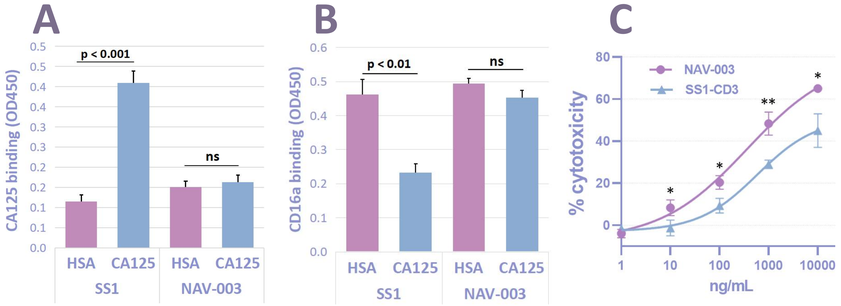
A) NAV-003 binds to MSLN's region III closest to the cell membrane. Other α-MSLN antibodies, such as SS1, bind to region I (96%) or region II (3%) and must compete with other factors, like CA125, for MSLN binding. B) NAV-003's configuration comprises an α-MSLN full-length IgG for optimal serum half-life + an α-CD3ε scFv component fused to IgG LC in an optimized configuration for T-cell activation.

Fig. 2 - NAV-003 elicits ADCC & IL-2 production by T cells



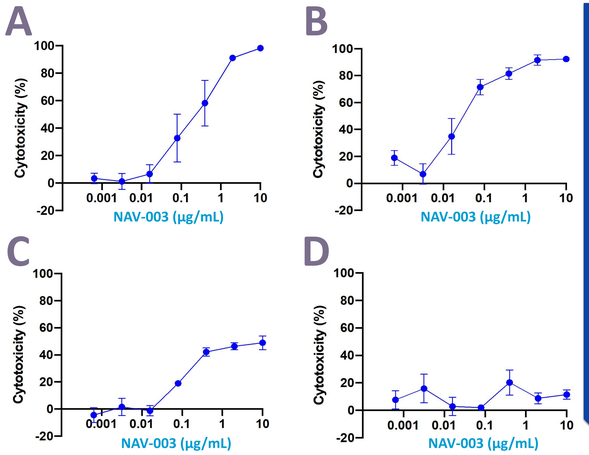
A) Antibody-dependent cellular cytotoxicity (ADCC) with human PBMCs: NAV-003 shows superior killing versus the parent α-MSLN IgG devoided of the α-CD3 arm. B) NAV-003 targeting MSLN-positive CHO cells elicits IL-2 production by human Jurkat T cells but not when targeting MSLN-negative CHO cells. No IL-2 production is elicited by the parent IgG.

Fig. 3 - NAV-003 is refractory to CA125 inhibition



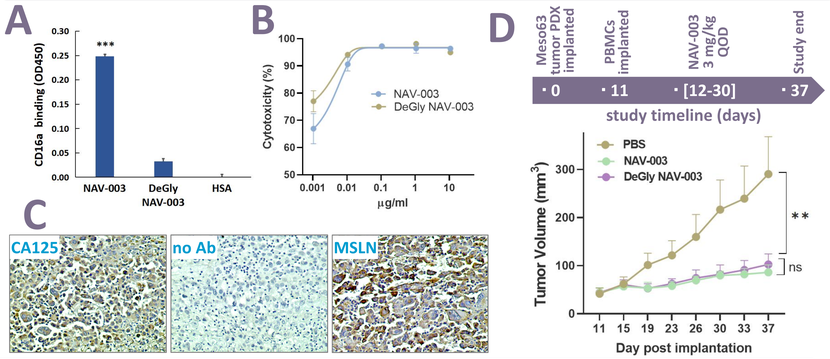
NAV-003 is refractory to CA125 binding (A) and shows unaltered CD16a engagement in the presence of CA125 (B), in contrast to the CA125-sensitive SS1 antibody. C) NAV-003 elicits greater cytotoxicity against CA125-positive OVCAR3 cells compared to SS1-CD3, a bispecific derived from SS1 antibody, which binds region I and is inhibited by CA125.

Fig. 4 - NAV-003 is active against mutliple cancers



NAV-003 shows broad PBMC-mediated cytotoxicity against MSLN-expressing tumor cell lines including OVCAR-8 (ovarian, panel A), NCI-meso63 (mesothelioma, panel B, and KLM-1 (pancreatic, panel C). These effects require MSLN expression as no killing was observed against the isogenic KLM-1-KO where MSLN expression was abolished via CRISPR (panel D).

Fig. 5 - NAV-003 α-tumor response in CA125$^+$/MSLN$^+$ PDX



A) Deglycosylated NAV-003 (DeGly) shows loss of Fc binding as planned B) DeGly NAV-003 still retains the ability to kill patient-derived mesothelioma (NCI-Meso63) by engaging human PBMCs via CD3. C) NCI-Meso63 PDX lesions express both CA125 and MSLN. D) *Top*, *in vivo study* outline. *Bottom*, both NAV-003 and DeGly NAV-003 show significant anti-tumor efficacy.