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The ADC NAV-001 targets a first-in-class mesothelin epitope, deploys a novel payload, and is refractory to CA125 inhibition

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Leaders in Humoral Immuno-Oncology

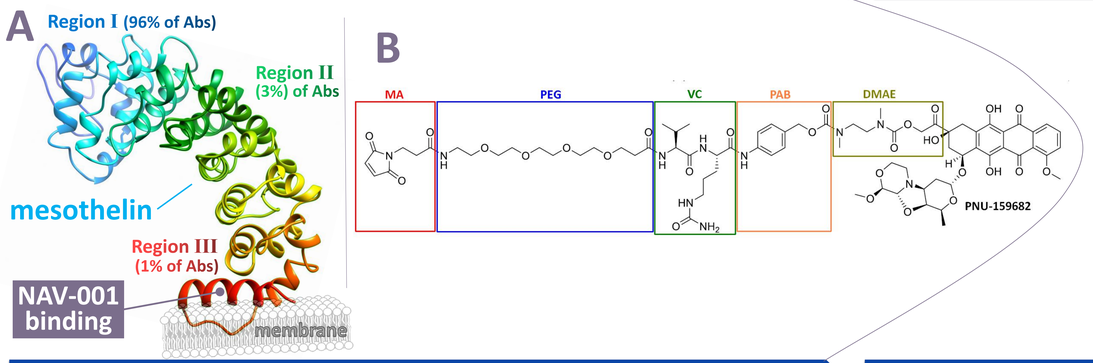
Mesothelin (MSLN) is a validated target – **A number of antibody therapeutics, vaccine and T-cell therapies targeting MSLN are in clinical evaluation, including antibody-drug conjugates (ADC) with traditional payloads DM4 or duocarmycin.**

New combinations of mAb-linker-payload are needed for maximal ADC performance – **NAV-001 deploys 1) the payload PNU-159682, a nemorubicin metabolite with 5 pM IC_{50} plus dual MoAs; 2) a cathepsin cleavable linker; 3) an α-MSLN mAb refractory to CA125 binding + targeting a unique MSLN epitope.**

NAV-001 is superior to other αMSLN ADCs affected by CA125 binding – **CA125 hinders the ADC uptake on tumor cells, whereas NAV-001, being refractory to CA125, exerts optimal cytotoxicity.**

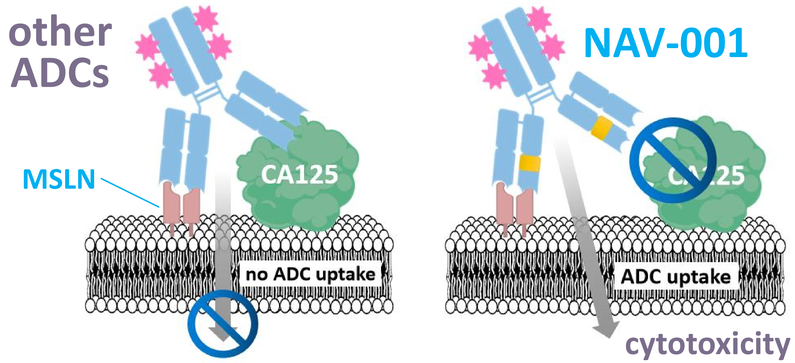
NAV-001 elicits tumor regression in PDX models – **sub-mg/kg dose levels can regress the growth of patient-derived tumors; Single-dose NAV-001 is effective at 0.75 mg/kg; Free payload at equivalent ADC dose level is unable to elicit response.**

Fig. 1 - NAV-001's unique epitope & payload



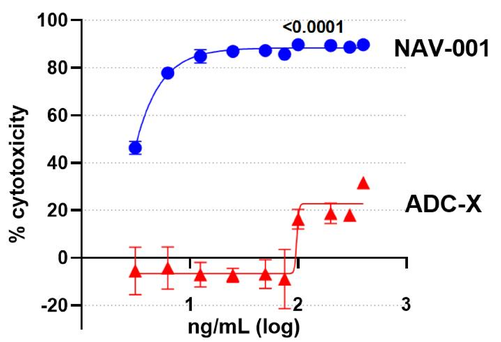
A) NAV-001 binds to MSLN's region III closest to the cell membrane, whereas most α-MSLN antibodies bind to region I (96% frequency) or region II (3%) and compete with other factors like CA125 for MSLN binding. B) Linker/payload in NAV-001 - N-maleoyl-B-alanine (MA), polyethylene glycol (PEG) valine-citrulline (VC); p-aminobenzylcarbamate (PAB); dimethylaminoethanol (DMAE); PNU-159682

Fig. 2 - NAV-001 is refractory to CA125



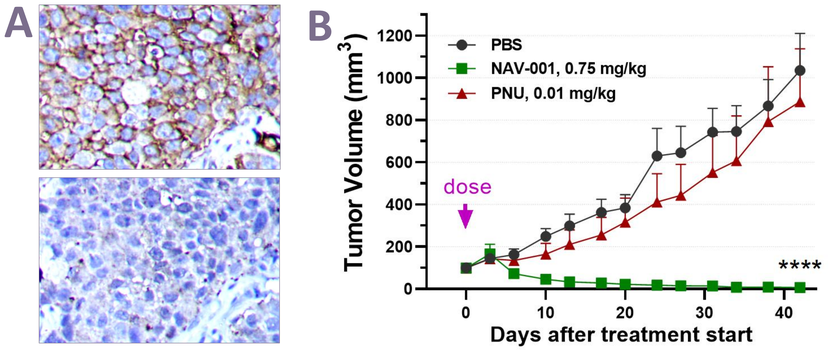
Left: Cellular uptake of other α-MSLN ADC candidates is hindered by CA125 binding, leading to their reduced potency in CA125+ tumor cells; Right: NAV-001, which lacks the CA125 binding motif (yellow), exerts optimal uptake and resulting cytotoxicity (below).

Fig. 3 - NAV-001 superior to other α-MSLN ADCs



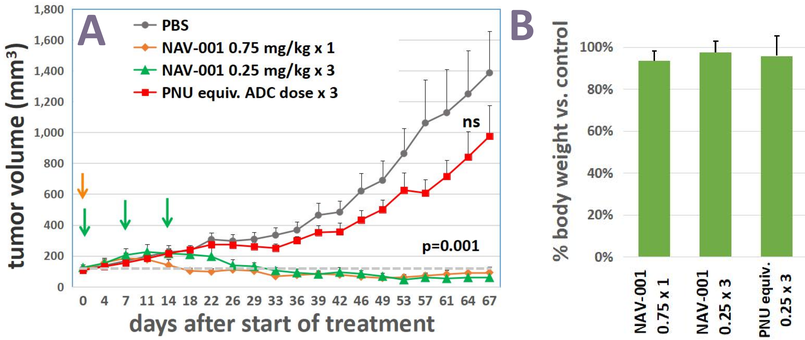
CA125+ and MSLN+ ovarian cancer cells were targeted with NAV-001 or ADC-X, an α-MSLN ADC clinical candidate reported in the literature. ADC-X, with its SPDB-DM4 linker/payload, showed weak killing effect, likely due to lower potency of DM4 vs. PNU and the CA125 inhibitory effect. In contrast, NAV-001 killing was robust at ≤100 ng/mL.

Fig. 4 - NAV-001 cures breast cancer PDX



A) Immunohistochemistry of patient-derived breast cancer (PDX) implanted in nude mice. Top, α-MSLN; Bottom, no antibody control. B) Single-dose 0.75 mg/kg NAV-001 achieved complete regression of established breast cancer PDX lasting >1 month. Free payload (PNU) at equivalent ADC dose was ineffective. No significant body weight loss were observed.

Fig. 5 - NAV-001 is superior to free payload



A) Mice with established patient-derived mesothelioma were treated with NAV-001 or unconjugated PNU-159682. NAV-001 at single dose (0.75 mg/kg) or weekly dose (0.25 mg/kg x 3) elicited tumor regression, while PNU-159682 at equivalent ADC dose (3 µg/kg) showed no significant response. B) NAV-001 was well-tolerated with no significant loss of body weight.