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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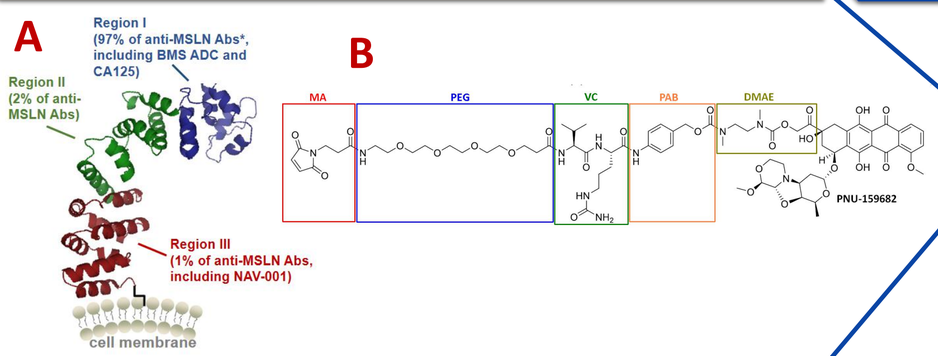
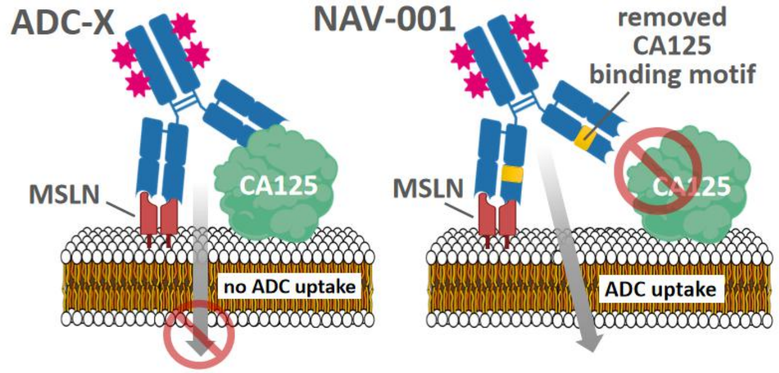
- ***Mesothelin (MSLN) is a validated target:*** A number of antibody therapeutics, vaccine and T-cell therapies targeting MSLN are in clinical evaluation, including antibody-drug conjugates (ADC) with traditional payloads DM4 or duocarmycin.
- ***New combinations of mAb-linker-payload are needed for 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; and 3) an αMSLN 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 as effective as 3 weekly doses; Free payload at equivalent ADC dose level is unable to elicit response.

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



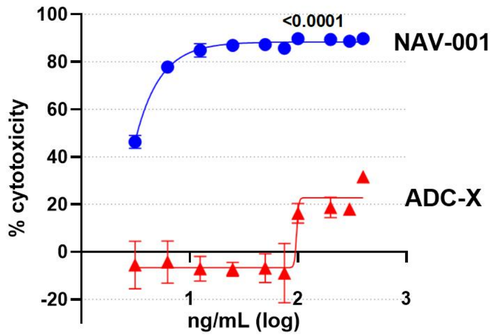
A) NAV-001 binds to MSLN's region III closest to the cell membrane, whereas other αMSLN antibodies bind to region I and compete with other factors like CA125 for binding. B) Linker/payload in NAV-001 - N-maleoyl-B-alanine (MA), polyethylene glycol (PEG) valine-citrulline (VC); p-aminobenzylcarbamate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

Fig. 2 - NAV-001 is refractory to CA125



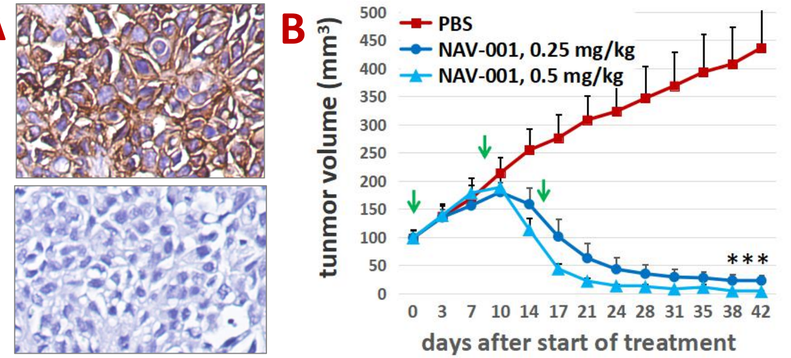
Left: Cellular uptake of ADC-X, an αMSLN ADC clinical candidate reported in the literature, is hindered by CA125 binding, leading to ADC-X reduced potency vs. CA125+ tumor cells; Right: NAV-001, which lacks the CA125 binding motif, exerts optimal uptake + cytotoxicity (below).

Fig. 3 - NAV-001 is superior to other αMSLN ADCs



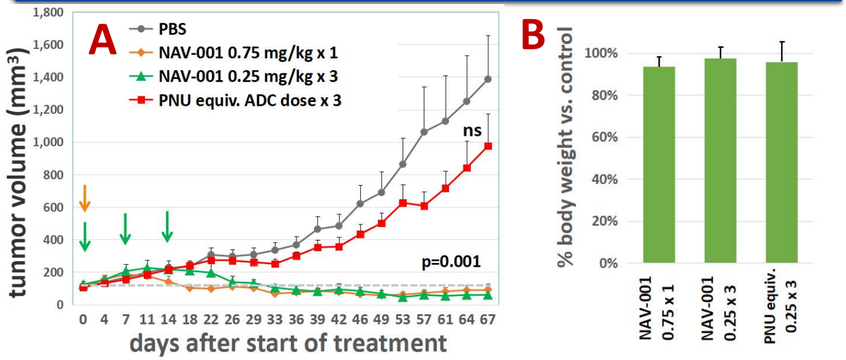
CA125+ and MSLN+ ovarian cancer cells were targeted with NAV-001 or ADC-X, an αMSLN ADC clinical candidate reported in the literature. ADC-X, with its SPDB-DM4 linker/payload, showed weak killing effect, likely due to lower potency of DM4 vs. PNU and the CA125 inhibitory effect. In contrast, NAV-001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

Fig. 4 - NSCLC PDX regression by NAV-001



A) Immunohistochemistry of patient-derived tumors implanted in nude mice. Top, αMSLN; Bottom, no antibody control. B) Mice with established patient-derived NSCLC lesions were treated with NAV-001 3 times weekly (arrows). NAV-001 elicited tumor regression that lasted at least 3 weeks after last dose. No significant body weight difference found among groups.

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 PNU159682 at equivalent ADC dose (3 μg/kg) showed no significant response. B) NAV-001 was well-tolerated with no significant loss of body weight.