#1303

Antibody drug conjugate (ADC) payload-induced IL1 suggests potential for anti-IL1RAP therapy combination for enhanced treatment efficacy and prevention of neuropathy

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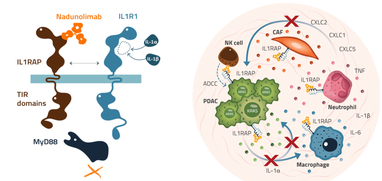
Introduction

Interleukin-1 receptor accessory protein (IL1RAP) is expressed in various solid tumors. It is essential for IL1 signaling via IL1α and IL1β, which promote tumor development as well as chemotherapy resistance.

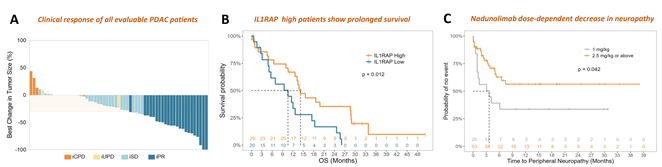
Chemotherapy can induce IL1 release — counteracts effects of therapy but also drives peripheral neuropathy, a common side effect of traditional chemotherapy.

Nadunolimab, a fully humanized monoclonal antibody, targets IL1RAP to kill tumor cells via antibody-dependent cellular cytotoxicity (ADCC) while simultaneously blocking IL1α/IL1β signaling. Clinical studies with nadunolimab suggest that targeting IL1RAP is not only promising for enhanced efficacy in combination with chemotherapy but also help alleviate neuroinflammation associated with chemotherapy-induced peripheral neuropathy (CIPN)[1,2].



Schematic figures of nadunolimab mode of action in the tumor microenvironment. *Nadunolimab binds to IL1RAP and blocks IL1 signaling. Nadunolimab also stimulates natural killer (NK) cells and destroy tumor cells via ADCC.*

In PDAC patients, nadunolimab in combination with gemcitabine/Nab-paclitaxel showed both promising target-dependent efficacy (overall survival of 14.2 months in IL1RAP high vs 10.5 months in IL1RAP low) and a dose-dependent reduction of CIPN[2].



Evaluation of efficacy and peripheral neuropathy in PDAC patients treated with nadunolimab in combination with gemcitabine/Nab-paclitaxel (NCT03267316)[2]. *Waterfall of tumor response in all evaluable patients (**A**): 23 (33%) patients had iPR as best overall response, 28 (38%) patients had iSD, 5 (7%) patients had iUPD, and 5 (7%) patients had iCPD; Patients with high IL1RAP expression showed significantly longer overall survival (OS) (**B**): Biopsies screened from 49 patients for IL1RAP expression on tumor cells. IL1RAP high patients showed significantly prolonged survival with median OS of 14.2 months compared to 10.6 months in IL1RAP low patients; Nadunolimab dose-dependent reduction in peripheral neuropathies (**C**): Dose groups 2.5-7.5 mg/kg were pooled and compared with 1 mg/kg dose group. The higher dose groups showed a lower incidence of any-grade peripheral neuropathy. Chemotherapy doses given were comparable between the dose groups.*

Aim

ADC payloads may function like traditional chemotherapy in inducing IL1, which would suggest potential synergisms between nadunolimab and ADC therapies, similar to those observed with chemotherapy[3]. To study the impact of ADC payloads on the IL-1 system, we assessed their effects on tumor cells, tumor cell co-cultures with cancer-associated fibroblasts (CAF), myeloid cells and on induction of peripheral neuropathy in a mouse model.

➢ **ADCs trigger IL1 release -** counteracts anti-tumor efficacy and induces neuropathy

➢ **Nadunolimab,** an antibody in clinical development, **blocks IL1 mediated signaling,** with effects on both tumor growth and chemotherapy-induced peripheral neuropathy[2]

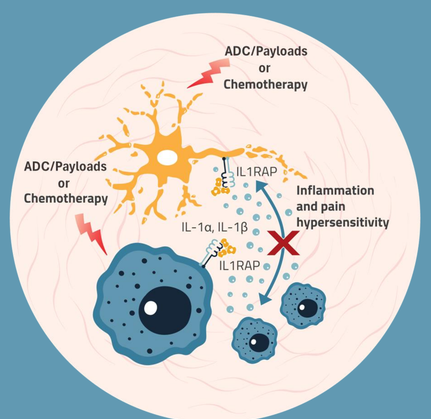
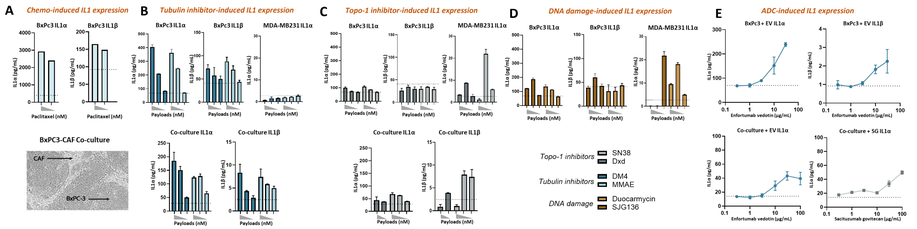


Figure represents ADC or chemotherapy-induced IL1 signaling. *ADC/payloads or chemotherapy promotes tumor growth and chemoresistance in the tumor but also neuroinflammation and neuropathy in the periphery.*

Nadunolimab combined with ADCs has potential for **improved therapy** offering both **neuroprotection** and **enhanced tumor regression**

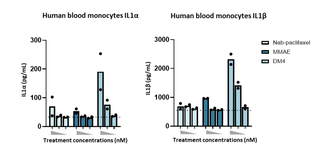
Results

Payloads and ADCs induce IL1 in cancer cell lines and cancer cells-CAF co-cultures



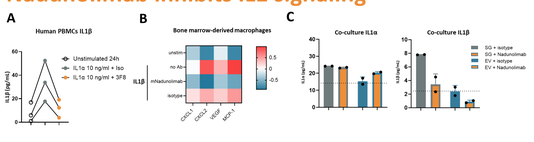
Induction of IL1 signaling by different classes of payloads in cancer cell lines and cancer cell-CAF co-cultures. *Treatment with paclitaxel in vitro induces IL1α and IL1β expression in BxPc3 cancer cell lines (**A**); Tubulin inhibitors (DM4 and MMAE) (**B**), Topo-1 inhibitors (SN38 and Dxd) (**C**), and DNA damage (Duocarmyin, or SJG136) (**D**) shows induction of IL1α and IL1β in BxPc3 and MDA-MB231 cancer cell lines and BxPc3–CAF co-cultures; ADCs such as Enfortumab vedotin (EV) and Sacituzumab govitecan (SG) induce IL1α and IL1β in BxPc3 cancer cell lines and BxPc3–CAF co-cultures (**E**). EV (MMAE-conjugated) targets Nectin-4 while SG (SN38-conjugated) targets TROP2 expression on tumor cells.*

Payloads induce IL1 in monocytes



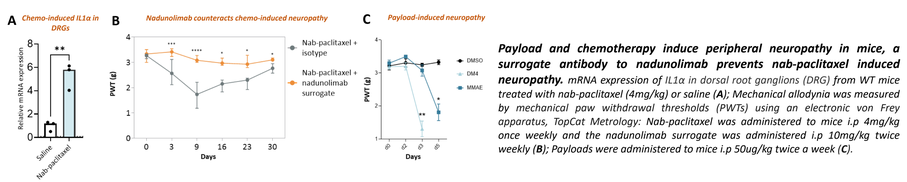
Induction of IL-1 in monocytes. *Nab-paclitaxel and payloads (MMAE and DM4) treatment shows a dose-dependent induction of IL1α and IL1β in human blood monocytes.*

Nadunolimab inhibits IL1 signaling



Nadunolimab inhibits IL1 signaling. *Nadunolimab (as 3F8; a chimeric murine IgG2a variant of the anti-human IL1RAP antibody) reduces IL1α-induced release of IL1β in human peripheral blood mononuclear cells (PBMCs) (**A**); Nadunolimab surrogate inhibits IL1β driven induction of chemokines in mouse bone marrow-derived macrophages (**B**); Nadunolimab inhibits ADC (EV or SG)-induced IL1α and IL1β in BxPc3–CAF co-cultures (**C**).*

Nadunolimab surrogate prevents neuropathy in mice



Payload and chemotherapy induce peripheral neuropathy in mice, a surrogate antibody to nadunolimab prevents nab-paclitaxel induced neuropathy. *mRNA expression of IL1α in dorsal root ganglions (DRG) from WT mice treated with nab-paclitaxel (4mg/kg) or saline (**A**); Mechanical allodynia was measured by mechanical paw withdrawal thresholds (PWTs) using an electronic von Frey apparatus, TopCat Metrology: Nab-paclitaxel was administered to mice i.p 4mg/kg once weekly and the nadunolimab surrogate was administered i.p 10mg/kg twice weekly (**B**); Payloads were administered to mice i.p 50ug/kg twice a week (**C**).*

Conclusions

- **Payloads and ADCs, similar to chemotherapy, induce IL1 from cancer cells, cancer cells-CAF co-cultures, and monocytes.**
- **Both chemotherapy and ADCs/payloads can induce neuropathy in mouse models; a nadunolimab surrogate antibody abrogates chemotherapy-induced neuropathy, inhibition of payload-induced neuropathy is currently investigated.**
- **Nadunolimab has the potential to inhibit IL1-driven tumor progression and chemotherapy-mediated resistance mechanisms while counteracting neuroinflammation leading to neuropathies.**

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References

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3. Blockade of IL-1α and IL-1β signaling by the anti-IL1RAP antibody nadunolimab (CAN04) mediates synergistic anti-tumor efficacy with chemotherapy Cancer Immunology, Immunotherapy 2023;72(3):667-678. doi: 10.1007/s00262-022-03277-3.