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BOOK OF ABSTRACTS

P021

LIGAND-INDEPENDENT TREM-1 BLOCKERS AS INNATE IMMUNE CHECKPOINT INHIBITORS TO OVERCOME CANCER IMMUNOTHERAPY RESISTANCE

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Since the first immune checkpoint inhibitor (ICI) was introduced in 2011, cancer immunotherapy has revolutionized the treatment of many types of advanced solid tumors. However, most patients still do not derive benefit. Notable examples are patients with pancreatic ductal adenocarcinoma (PDAC). These patients show no or poor response to standard anti-PD-1/PD-L1 and anti-CTLA-4 immunotherapies. A growing line of evidence suggests that overexpression of triggering receptor expressed on myeloid cells 1 (TREM-1) in tumors correlates closely with infiltration of immune-suppressive cells, immune regulation, and poor clinical outcome, highlighting TREM-1 as a novel innate immunity target for cancer immunotherapy. To block TREM-1, we developed a TREM-1 inhibitory peptide sequence GF9 that employs a novel, ligand-independent mechanism of action, addressing the problem of the unknown TREM-1 ligand(s). Here, we demonstrated that well-tolerable GF9 sequence-based TREM-1 inhibitors reduce inflammation and tumor-associated macrophage (TAM) content, inhibit tumor growth, and overcome resistance to anti-PD-L1 immunotherapy in mouse models of PDAC.

Free GF9 peptide and macrophage-targeted lipopeptide complexes of GF9 sequence-based TREM-1 inhibitory peptides were synthesized and characterized in biophysical, biochemical, and cell-based assays. Mouse studies were performed using subcutaneous human AsPC-1, BxPC-3, CAPAN-1, MIA PaCa-2, and PANC-1 xenograft athymic nude mouse models as well as a fully immunocompetent mouse model of PDAC generated by inoculation of the primary bioluminescent (a firefly luciferase, Luc, expressing) Kras (G12D)/Trp53 null/Pdx1-cre (KPC) mouse tumor chunk into the subcapsular region of the pancreas of wild-type C57BL6 mice. In the xenograft models, TREM-1 inhibitors were intraperitoneally (i.p.) injected at various doses once a day for 5 days per week for 30 days on average, and tumors were measured twice weekly until sacrifice. TAM content in xenografts was measured by F4/80 immunostaining and serum cytokines were analyzed by commercially available ELISA kits. In the syngeneic orthotopic model, TREM-1 inhibitors were i.p. administered at various doses once a day for 21 days either alone or in combination with an anti-mouse PD-L1 antibody i.p. administered at a 10 mg/kg dose twice a week for 3 consecutive weeks, and tumor progression was monitored using IVIS® bioluminescent imaging on days 4, 8, 11, 15, 18, and 22.

Ligand-independent TREM-1 blockers alone inhibited tumor growth and extended survival in xenograft and syngeneic models of PDAC. In the xenograft models used in these studies, TREM-1 blockade substantially suppressed the release of serum proinflammatory cytokines (interleukin-1alpha, IL-1a, and IL-6) and macrophage colony-stimulating factor (M-CSF or CSF-1), and reduced the intratumoral macrophage content. Furthermore, the higher TAM content in xenografts, the higher was the efficacy of the TREM-1 inhibitory formulations tested. In the syngeneic orthotopic mouse model of PDAC, ligand-independent blockade of the TREM-1 signaling pathway significantly inhibited tumor progression and substantially improved the therapeutic efficacy of PD-L1 blockade compared with TREM-1 inhibitor and anti-PD-L1 treatments alone.

These data further confirm that TREM-1 plays an important role in the pancreatic cancer pathogenesis and suggest that ligand-independent TREM-1 inhibition represents a novel strategy to overcome immunotherapy resistance in patients with PDAC. In line with several recent independent studies that demonstrated that TREM-1 inhibitory peptide GF9 sensitizes hepatocellular carcinoma to immunotherapy in different syngeneic mouse models, this suggests that ligand-independent

TREM-1 blockers can be developed into a new class of innate ICIs aimed to overcome resistance of poorly sensitive tumors to current cancer immunotherapies.