411 Polyamine Transport Inhibitors As Immunometabolic Adjuvants

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Preclinical
Target(MoA)	Polyamine transport inhibitors (PTIs)
Brief Description	• Novel proprietary small molecules that act as polyamine transport inhibitors (PTIs) or polyamine-drug conjugates (transport-based poisons) • These two strategies exploit the highly upregulated polyamine transport system in cancer, either by direct blockade or as a 'Trojan Horse' attack • In preclinical studies, these strategies safely and effectively debulk tumors • Mechanistic studies show that the therapies work chiefly by eradicating myeloid-derived suppressor cells that mediate immunosuppression • Preclinical studies have demonstrated general anti-tumor efficacy in multiple experimental tumor systems, including melanoma, breast, ovarian, colorectal and pancreatic cancers • General utility to safely heighten the anti-cancer efficacy of combination chemotherapy, molecular targeted therapy and immunotherapy
Organization	Lankenau Institute for Medical Research

Differentiation

□ **Polyamine transport as an anticancer therapeutic target**

- Elevated levels of polyamines is associated with cell proliferation in both normal and neoplastic tissues. Compared to normal cells, tumor cells have been shown to contain elevated levels of polyamines in order to meet their huge metabolic needs
- Oncogenes such as MYC and RAS both upregulate polyamine biosynthesis and increase cellular uptake of polyamines by inducing the polyamine transport system (PTS)
- A hallmark of tumorigenesis involves the induction of ornithine decarboxylase (ODC), the initial rate-limiting enzyme in polyamine biosynthesis
- Use of transgenic mouse models has demonstrated that increased ODC activity is sufficient to promote tumor development following low dose exposure to carcinogens, UV irradiation, or oncogene activation and wounding
- AMX-513 (combination of two drugs, a polyamine synthesis inhibitor (DFMO, difluoromethylornithine) and a polyamine uptake, or transport, inhibitor (AMXT-1501), Aminex Therapeutics): Phase 1 (2018 May~) for neuroblastoma, oral administration
- LIMR and UCF scientists who are leaders in the field have synthesized and characterized novel proprietary small molecules that act as PTIs or polyamine-drug conjugates (transport-based poisons)

□ **Unmet need & opportunity in cancer immunotherapy**

- A great need exists for cancer therapies that can eradicate immune myeloid suppressor cells that block the efficacy of cancer immunotherapeutics, such as immune checkpoint drugs
- The therapies work chiefly by eradicating myeloid-derived suppressor cells that mediate immunosuppression and may offer a general approach to heighten immune responses in cancer

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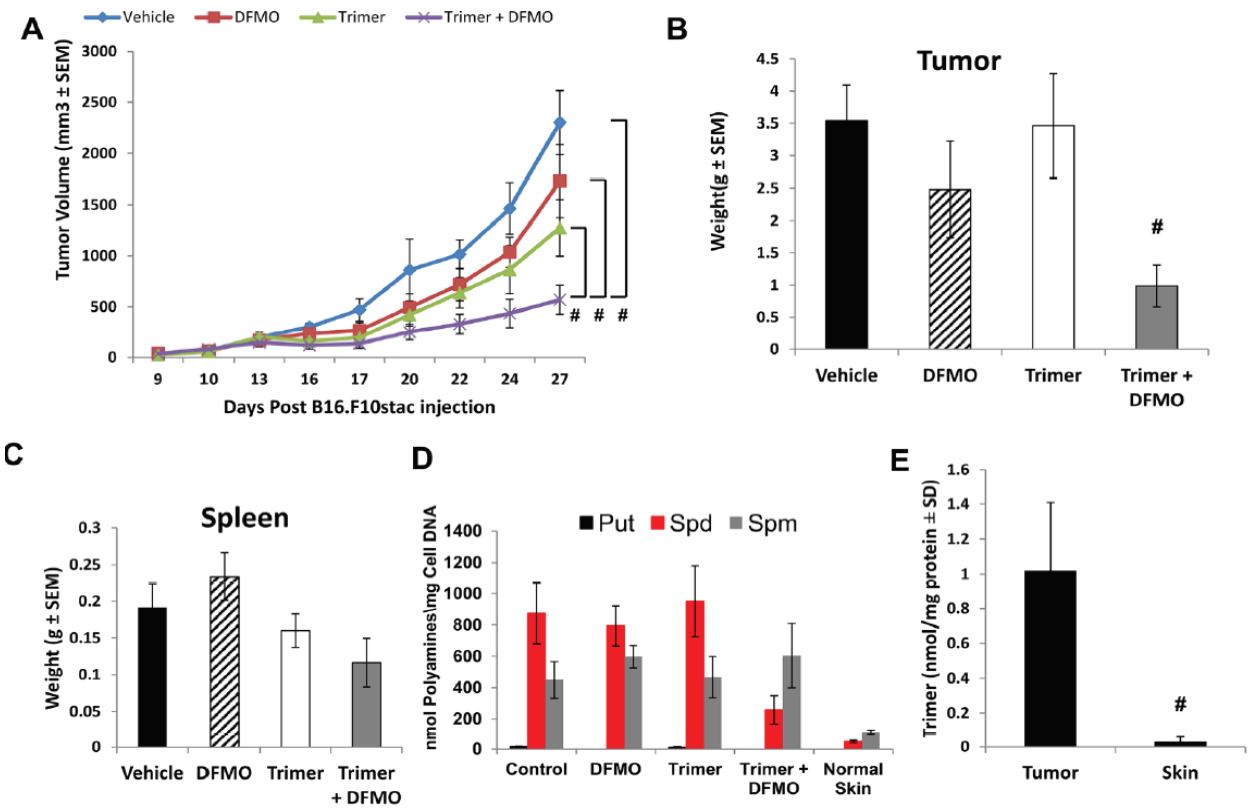
Key Data

Anti-tumor effect of polyamine starvation via both inhibiting polyamine biosynthesis and blocking the upregulated import of polyamines into the tumor

B16F10-sTAC (melanoma) tumor growth inhibition with DFMO (ODC inhibitor) and Trimer PTI (novel polyamine transport inhibitor)



(A) Mice were subcutaneously injected with 5x105 B16F10-sTAC melanoma cells. When tumors were 50-100 mm3 in size, treatment was initiated with either saline, 0.25% DFMO (w/v) in the drinking water, Trimer PTI (i.p., 3 mg/kg, once a day) or both DFMO and Trimer PTI. (B) Spleen weight was determined upon sacrifice (mean ± SEM). (C) Upon sacrifice, tumors were excised and weighed (mean ± SEM). (D) Polyamine levels were determined in tumors by HPLC and normalized to DNA levels in the tissue extracts (nmol/mg DNA). (E) Tumor and non-tumor bearing skin tissues were excised from PBT-treated mice, flash frozen, finely pulverized in liquid nitrogen with mortar and pestle, homogenized in a solution of 33% water, 66% methanol and 1% acetic acid, and then centrifuged at 5000 rpm for 10 min at 25˚C. Trimer PTI levels were determined in tumor and skin supernatants by mass spectrometry and normalized to tissue protein concentration (nmol/mg protein). n = 5-10 mice per group; * = $p \leq 0.05$ and # = $p \leq 0.01$ compared to vehicle-treated mice.

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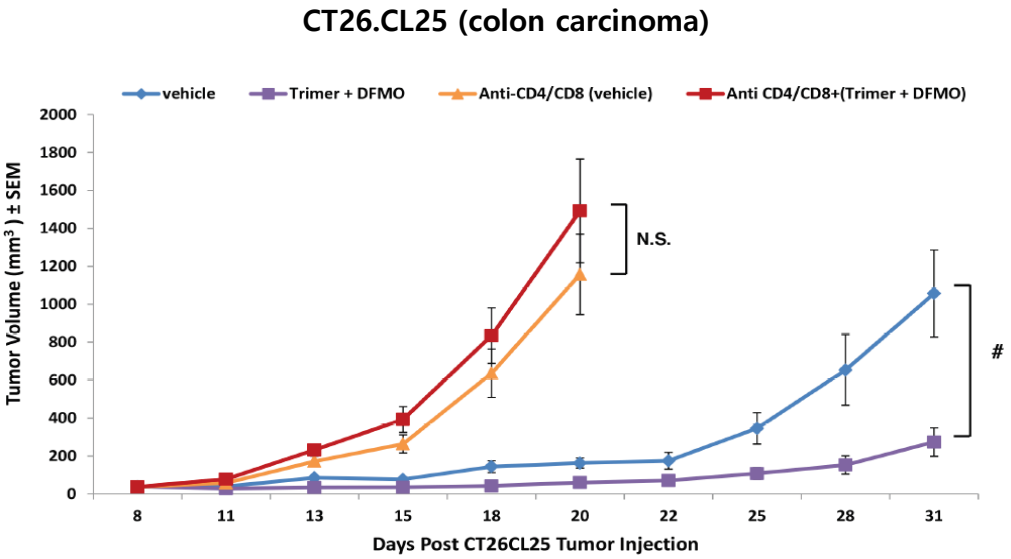
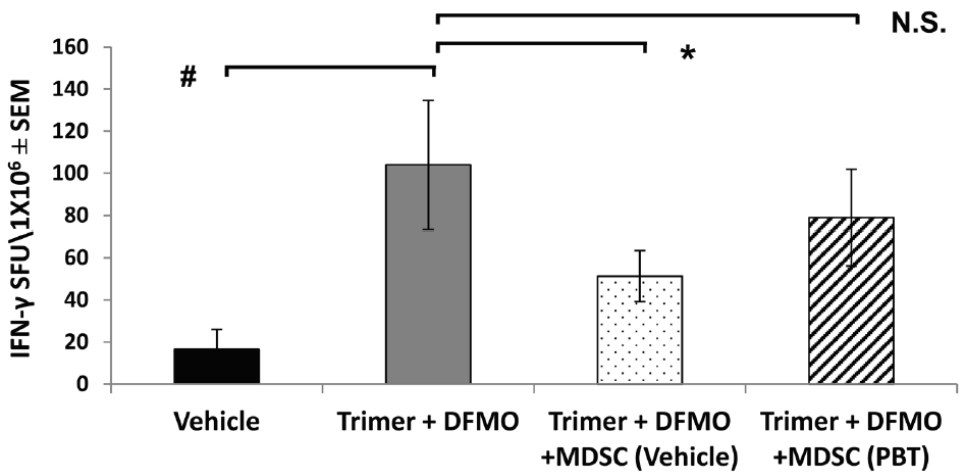
Depletion of CD4+ and CD8+ T-cells reverses PBT inhibition of tumor growth



DMice were subcutaneously injected with 5x105 CT26.CL25 colon carcinoma cells. When tumors were 50-100 mm3 in size, treatment was initiated with either saline or 0.25% DFMO (w/v) in the drinking water plus Trimer PTI (i.p. 3 mg/kg, once a day). Mice in the anti-CD4/CD8 groups were i.p. injected with 75 µg of anti-CD4 and anti-CD8 antibodies every three days starting 3 days prior to the initiation of treatment with a total of four doses.

Co-treatment with DFMO and Trimer PTI decreases the immunosuppressive activity of MDSCs



One week prior to sacrifice, MDSCs were isolated from the spleens of CT26.CL25 tumor-bearing mice that were treated either with vehicle or Co-treatment with DFMO and Trimer PTI decreases. Isolated MDSCs (5.2 x 106 per mouse) were then adoptively transferred into separate groups of recipient tumor-bearing mice in the PBT-treated group. Upon sacrifice, splenocytes from the recipient mice were used to measure the frequency of IFN-γ producing T-cells.

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Intellectual Property

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