DISTINCT EFFICACY AND IMMUNOLOGICAL RESPONSES TO α PD-1, α PD-L1 AND α PD-L2 IMMUNOTHERAPY IN AGED VERSUS YOUNG HOSTS

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Background Aging is the biggest risk factor for cancer, yet there are limited pre-clinical/clinical data regarding aging effects on immune checkpoint (IC) inhibition (ICI) outcomes. α PD-1 can potentially block PD-L1 and PD-L2 while α PD-L1 can block PD-1 and CD80. Melanoma response to α PD-1/ α PD-L1 correlates with CD8+TCF-1+ T cell stem cell (TCSC) generation.¹ Lack of host IL-17 can lead to increased IFN- γ production.^{2,3}

Methods We tested α PD-1 (200 μ g/mouse), α PD-L1 (100 μ g/mouse) or α PD-L2 (200 μ g/mouse) in aged (18–33 months) and young (3–8 months) mice challenged orthotopically with B16 (WT or PD-L1ko) or TPN61R melanoma (NRAS mutation melanoma model)⁴ (α PD-L2 only) (SQ). Tumors were analyzed by flow. We tested α PD-L2 (20 μ g/ml) effects by co-culturing young or aged T cells $\pm$ young or aged myeloid cells.

Results We reported that α PD-1 treats young and aged with B16 whereas α PD-L1 treats young not aged.⁵ α PD-L2 treated B16 and TPN61R melanoma in aged but, remarkably, not young, the first single agent anti-cancer immunotherapy exhibiting this property (figure 1). B16 tumors from aged had differential IC content (PD-1, PD-L1, CD80, PD-L2) versus tumors from young (e.g., more PD-L2+ tumor and stroma cells in aged mice; figure 2). Efficacy in young (α PD-1, α PD-L1) and aged (α PD-L2) correlated with increased tumor TCSC content (figure 3). α PD-L2 efficacy against B16 in aged mice required host IFN- γ and IL-17 (figure 4). α PD-1 efficacy against B16 in aged appeared to be host and tumor PD-L1 independent (figure 5). PD-L1KO B16 response to α PD-1 in aged also correlated with increased tumor TCSC content. Myeloid cell PD-L2 signaling inhibited aged but not young CD8+ T cell IL-2 production in vitro (figure 6).

Abstract 234 Figure 1

Abstract 234 Figure 2

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Abstract 234 Figure 6

Conclusions Treatment differences in aged versus young could depend on IC, TCSC and/or host cytokine differences (IL-17/IFN- γ). α PD-1 efficacy in aged PD-L1KO mice challenged with PD-L1KO B16 suggests that PD-L2 block is sufficient for α PD-1 efficacy in aged. PD-L2 expression differences in the tumor microenvironment could also contribute to treatment efficacy differences. PD-L2 inhibitory signaling on aged but not young CD8⁺ T cells is a likely mechanism for α PD-L2 efficacy in aged but not young. We are now testing the role of IL-17 in α PD-L2 efficacy as it could be upstream of IFN- γ effects, and TCSC effects in aged versus young. Our work can improve cancer immunotherapy in aged hosts and provides insights into treatment failure, including in young hosts.

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Ethics Approval All animal studies are approved by UTHSA IACUC.

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