ANTI-PDL2 USES IL17-DRIVEN INTERFERON-GAMMA TO TREAT AGED BUT NOT YOUNG CUTANEOUS MELANOMA-BEARING MICE, AND TREATS OTHER TUMORS IN AN AGE- AND TME-DEPENDENT MANNER

Myrna Garcia, Yilun Deng, Clare Murray, Carlos Ontiveros, Alvaro Padron, Sujadana Skopelija-Gardner, Kah Teong Soh, Dhan Chand, Tyler Curiel
UT Health San Antonio, San Antonio, TX, United States; Dartmouth, Lebanon, NH, United States; Agents, Lexington, MA, United States; Dartmouth Health, Lebanon, NH, United States

Background Immune checkpoint blockade (ICB) with αPD1, αPDL2, αCTLA4 and αLAG3 is FDA-approved but agents fail to treat up to ~80% of all cancers. PDL2 is a second PD1 ligand but little is reported on αPDL2 cancer immunotherapy. Age is the biggest risk for cancer, yet little few age affects on ICB are reported. We previously reported that αPD2 treats melanoma in aged but not young mice. Here we provide mechanistic insights, outcomes and mechanisms in other cancers and human data.

Methods We tested αPDL2 ICB and mechanisms in WT, IFNγKO and IL17KO mice in B16F10 (B16) and Nras mutated melanomas, ID8agg ovarian cancer and MB49 bladder cancer. We tested αPDL2 in aged (18-33 months) and young (3-8 months) mice. Tumors were analyzed by flow cytometry plus UMAP. Human PBMC and tumor samples were from commercial and institutional sources. TCGA data were mined.

Results αPDL2 ICB was ineffective in young mice with transplanted SQ B16 or NRAS-mutated melanoma, but remarkably effective in both in aged. αPDL2 efficacy was host IFNγ-dependent as expected, but also unexpectedly host IL17-dependent, which induced IFNγ. αPDL2 promoted IFNγ production by CD8+, CD4+ and γδ T cells and induced Treg fragility all in a host IL17-dependent manner. A cellular IL17 source for αPDL2 efficacy, mechanism for age-related IL17-driven IFNγ and contributions from Treg fragility are under study but not yet established. αPDL2 failed to treat transplanted orthotopic ovarian cancer in young or aged, but treated young mice bearing transplanted heterotopic, SQ bladder cancers, demonstrating αPDL2 is not efficacious only in aged or melanoma and that young skin is not necessarily hostile to αPDL2. TCGA data showed IL17 and PDL2 expression significantly increases by age in all cancers generally and specifically in melanomas. PDL2 protein increase by age was confirmed in human PBMC and primary tumors in lin-DR⁺CD141⁺ cDC1 but not on cDC2, plasmacytoid DC or other myeloid cells, T cells or B cells by flow cytometry. Both TCGA and flow data sets corroborated mouse data.

Conclusions αPDL2 is effective in aged but not young melanoma-bearing hosts and requires IL17 for efficacy. IL-17 is necessary for improved IFNγ production which is a likely αPDL2 efficacy mechanism. αPDL2 is a promising ICB approach meriting additional studies of mechanisms and effects on distinct tumors and TME. As age effects were confirmed in humans, it could be especially useful in aged hosts, or selected ICB failures (e.g., αPDL1) as we previously reported.

Acknowledgements Funding: This research was funded by the NIH M. G. (T32GM111389, TL1 TR002647), Y. (CPRIT Research Training Award [RP 170345] and Ovarian Cancer Research Alliance Ann and Sol Schreiber Mentored Investigator Award), C. M. and C.O. (T32GM113896) The Clayton Foundation (no grant number) and the NCI (CA204965, CA054515, CA231325) supported Curiel. This work was supported by the Flow Cytometry Shared Resource Facility, UL1 TR001120

REFERENCES

Ethics Approval This study obtained IACUC approval, from UTHSA (20180021AR)