improved the effector properties of T cells via decreasing expression levels of co-inhibitory molecules and decreasing frequency of regulatory T cells (figure 6). Clinically, VIPR1 receptor expression, but not VIP, provides a survival benefit (figure 7).

Conclusions VIP is a targetable mechanism of immune escape in PDAC. Inhibiting VIP receptor signaling improves effector properties of T cells and synergistically improves the anti-tumor response to checkpoint inhibitors in mouse PDAC models.

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820 MCLA-145 IS A BISPECIFIC IGG1 ANTIBODY THAT INHIBITS PD-1/PD-L1 SIGNALING WHILE SIMULTANEOUSLY ACTIVATING CD137 SIGNALING ON T CELLS

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Background MCLA-145 is a CD137 x PD-L1 bispecific antibody that releases PD-L1 mediated T-cell inhibition and activates and expands T cells through agonism of CD137. Immune checkpoint inhibitors (ICI) against PD-(L)1 have demonstrated anti-tumor efficacy in a fraction of patients across a broad range of cancers. CD137 (4-1BB, tumor necrosis factor receptor superfamily 9) is an inducible costimulatory receptor transiently expressed on T cells after TCR engagement. CD137 signaling is triggered by receptor clustering and leads to enhanced cytokine production; T cell proliferation, survival, and effector function; and immunological memory formation. Targeting of PD-L1 and CD137 with MCLA-145 may achieve synergistic activity by simultaneously blocking the inhibitory checkpoint PD-L1 and activating tumor specific T cells through co-stimulation.

Methods We performed combinatorial functional screening of bispecific antibodies generated from high affinity inhibitory Fabs binding PD-L1 combined with a large and diverse panel of agonistic CD137 Fabs.

Results MCLA-145 was selected based on its in vitro potency in multiple primary human immune cell assays. Further, it displays an ability to reverse T cell suppression mediated by M2 macrophages or Tregs. MCLA-145 binds to a unique epitope in the cysteine rich domain 2 of CD137 that overlaps with the CD137L binding region, and all potent bAbs in the screen were able to bind to this region. MCLA-145 drives activation of CD137 and the degree of CD137 agonistic activity in T cells correlated with the expression level of PD-L1 on neighboring cells. Using proximity ligation assays and confocal microscopy we demonstrated that MCLA-145 clusters CD137 on the surface of T cells resulting in internalization. The binding location of MCLA-145 on CD137 may be optimal for the formation of 'immunological synapses' with PD-L1 expressing antigen presenting cells or tumors resulting in the potent activation of tumor specific cytotoxic T cells.

Conclusions These experiments demonstrate the dual anti-cancer activity of MCLA-145 in preclinical models: release of T-cell checkpoint inhibition through PD-L1; and activation and expansion of T cells through CD137, therefore overcoming T-cell exhaustion and increasing T-cell presence/activity (infiltration) in tumors. MCLA-145 is currently undergoing clinical development in an ongoing trial (NCT03922204).

Ethics Approval Animal experiments were performed according to guidelines for animal care of the local Animal Experiments Committee; Use of human blood cells from healthy volunteers was approved by the blood bank's Ethical Advisory Council.

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821 CLASS SPECIFIC HDAC INHIBITION DIFFERENTIALLY AFFECTS THE FUNCTION OF SPECIFIC T CELL SUBSETS

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Background Histone deacetylase inhibitors (HDACi) are currently being used in the clinic to treat a variety of cancer types. Despite their wide use, the mechanism by which they exert anti-tumor effects is largely unknown. Although originally posited to abrogate tumor proliferation via regulating tumor suppressor genes, responses to monotherapies of HDACi have been shown to be dependent on an adaptive immune system and to enhance responses to immunotherapy. However, whether this mechanism is driven by enhancing tumor immunogenicity or enhancing anti-tumor immune responses is unclear. Understanding this could help identify optimal combination regimens for augmenting immunotherapies. Given the role of epigenetics in regulating T cell differentiation upon antigen encounter into discrete subsets, these studies sought to determine whether HDACi differentially impact naïve from memory T cell subsets.

Methods PBMCs from healthy donors were stimulated with either anti-CD3/anti-CD28 or PMA/Ionomycin in the presence or absence of different HDAC inhibitors (OKI-005, 250 nM; Entinostat, 5 uM; and Vorinostat, 1 uM). Cells were evaluated at different time points by flow cytometric analysis to compare responses by T cell subsets for changes in cytokine production, protein acetylation and other functional responses. Supernatant was collected in separate experiments for comprehensive cytokine bead arrays.

Results Cytokine analysis of supernatants showed clear differences in response to HDACi as while most cytokines decreased, others were either unaffected or increased. We next performed ICS with surface markers to determine if these changes in cytokine production levels were subset specific. Comparisons of naïve and memory subsets found decreased IL-2 levels was primarily attributed to loss of production by naïve T cells. Furthermore, gain of TNFa was almost completely restricted to naïve cells. The preferential responses by naïve T cells was further verified during global changes in acetylated protein levels. Lastly, we found differences between