Background The signaling pathways involving phosphoinositide-3-kinases (PI3Ks) are highly conserved and tightly regulated to influence the activation, proliferation, and survival of all cell types. PI3K signaling plays a major role in T cell responses to antigen due to its position directly downstream of T cell receptor (TCR)/CD28 ligation. Our lab has shown that the cell surface protein TrIP (Transmembrane Inhibitor of PI3K, gene name: Pik3ip1) has a distinctly high expression on T cells and is capable of regulating PI3K signaling in T cells, acting as a negative regulator of T cell immune responses. These studies revealed that CD4+ T cells lacking TrIP expression exhibit a more Th1 inflammatory phenotype compared to WT T cells, both in vivo and in vitro. These data have led us to propose that TrIP restricts the inflammatory activity of T cells, including CD8+ T cells, and that targeting/knockout of this negative regulator may promote antitumor immunity.

Methods Using a novel conditional TrIP knockout mouse model developed in house, we have performed syngeneic tumor challenges in CD8+ T cell-specific TrIP knockout mice (TrIPfl/flE8icre). We have also characterized the tumor immune infiltrate of these mice to understand the impact of T cell-specific TrIP deficiency on the immune landscape.

Results Our data show that CD8+ T cell-specific TrIP knockout mice (TrIPfl/flE8icre) are resistant to growth of syngeneic tumors. In addition to increased tumor resistance, we have also found that tumors harvested from our TrIPfl/flE8icre knockout mice contain twice as many infiltrating T cells compared to their WT counterparts. We also found that CD8+ T cells are the major drivers of this infiltration, and importantly don’t display any increase in exhaustion.

Conclusions We describe data demonstrating that TrIP, a relatively novel PI3K inhibitor uniquely expressed on the surface of T cells, plays a significant role in the antitumor immune activity of CD8+ T cells. Our CD8+ T cell-specific TrIP knockout mice are resistant to tumor challenge and show more robust tumor CD8+ T cell infiltration. We are hoping for future/ongoing adoptive transfer experiments will help elucidate if TrIP knockout promotes infiltration/proliferation/survival within the TME. Nevertheless, we propose TrIP as an exciting novel immunotherapeutic target worthy of further investigation.

REFERENCES