Background: Cancer has chronic antigen exposure that results in a suppressed CD8 T cell state termed exhaustion. An outcome of anti-PD-1 blockade therapy is the expansion of early exhausted CD8+ T cells into a terminally differentiated exhausted state. The reversal of this transcriptionally plastic yet epigenetically fixed state of CD8 T cell exhaustion has the potential to increase responses to anti-PD-1 therapy.

Methods: CX3CR1 is a marker of CD8 T cell activation, effector function however less is known about the contribution of CX3CR1 in CD8 T cell exhaustion. We identified three distinct subsets of CD8+ tumor infiltrating lymphocytes (TILs) based on high, mid, and negative CX3CR1 expression in a mouse model of colon carcinoma.

Results: The CX3CR1 high CD8+ T cells are more exhausted with higher PD1+TIM3+ expression compared to CX3CR1 mid and CX3CR1 negative cells thereby representing the terminal state of CD8 T cell exhaustion. Moreover, CX3CR1 high CD8 T cells increase following anti-PD-1 blockade, and their abundance is associated with a positive response to anti-PD-1.

Conclusions: We identify a consequence of CX3CR1 in terminal T cell exhaustion, and our work can offer strategies to increase responses to anti-PD-1.

Ethics Approval: Animal experiments were performed as per the IACUC regulations at the Dana Farber cancer Institute, and the MD Anderson Cancer Center.