Multiple mechanisms of tumor-induced immune escape contribute to the failure of spontaneous or vaccine-induced immune T cell responses to promote tumor regression in humans. We observed that tumor antigen (TA)-specific CD8+ and CD4+ T cells present at periphery and at tumor sites in patients with advanced melanoma co-express a number of inhibitory receptors (IRs) including PD-1, BTLA, Tim-3 and TIGIT. These IRs bind to their ligands expressed by antigen-presenting cells and tumor cells in the tumor microenvironment (TME). Combinatorial blockades with anti-PD-1 antibody and either anti-BLTA, anti-Tim-3 or anti-TIGIT antibodies appeared superior to each single blockade in enhancing the expansion and function of dysfunctional TA-specific T cells present at the periphery and at tumor sites, suggesting that these inhibitory pathways are non redundant. Interestingly, a number of IRs are highly expressed by functional vaccine-induced T cells in patients with advanced melanoma and regulate their expansion. Immune checkpoint blockade enhanced the proliferative capacities and functions of vaccine-induced TA-specific T cells in vitro, supporting the implementation of cancer vaccines trials with immune checkpoint blockade. Most recently, we have observed that cytokines produced in the TME cooperate with PD-1 to impede the survival of TA-specific T cells, suggesting that cytokine blockade adds to PD-1 blockade to reinvigorate dysfunctional TA-specific T cells.

Collectively, our findings suggest that a number of novel therapeutic strategies counteracting negative immunoregulatory networks in the TME add to PD-1 blockade to stimulate potent TA-specific T cell responses and increase the likelihood of clinical benefits.