Recent investigation into immunoregulatory roles of both TIGIT and PD-1 T cell receptors reveals that their suppressive effects converge with the inhibition of another T cell receptor, CD226. Co-blockade of these receptors reduced tumor volume in vivo and shows potential as a promising new cancer immunotherapy.

It has been established that tumors often evade the immune system through the modulation of immune checkpoint pathways. Understanding these pathways and the immunoregulatory receptors involved provides crucial insight into the development of novel, more effective anticancer treatments. During the immune system’s tumor surveillance, the activity of CD8+ cytotoxic T cells is initiated when the T Cell Receptor (TCR) recognizes and binds with antigen-bound Major Histocompatibility Complex 1 (MHC-1) on the surface of infected or cancerous cells. Under normal circumstances, subsequent activation of these cytotoxic T cells initiates a release of cytokines and catabolic enzymes that lead to apoptosis of the target cell. While the TCR and MHC molecules have been identified as key components in this process, several co-signaling molecules have also been revealed to be integral players in T cell regulation. These receptors have been shown to both promote and inhibit the activation of T cell immune responses. However, the mechanisms through which most of these co-signaling molecules act are still unknown.

One such set of co-signaling molecules is the Programmed Death-1 (PD-1) Receptor and its ligand, PD-L1. These inhibitory immunoregulators play a role in autoimmunity and suppression of the immune system during pregnancy. Interestingly, it has been observed that certain tumors have increased expression of PD-L1. In these scenarios, during the initial stimulatory TCR:antigen:MHC-1 interaction, PD-L1 on the cancer cell binds to PD-1 on the T cell and inhibits any further activity. This suppression allows the tumors to grow and spread, unseen by the immune system (Figure 1a).3 New cancer immunotherapy research has demonstrated promising outcomes with the use of Immune Checkpoint Blockade (ICB) therapy. In these novel therapies, specific monoclonal antibodies selectively block the action of inhibitory co-signaling molecules. Recently published research by Banta et al. suggests co-blockade of the T cell inhibitory receptors PD-1 and a relatively novel T cell Immunoreceptor with Ig and ITIM domains (TIGIT) as a new anti-cancer therapeutic.4 This work investigated the synergistic effects of blocking the aforementioned PD-L1:PD-1 interaction combined with the blockade of TIGIT. (Figure 1b) The aim of this research was to study the mechanisms by which anti-PD-1 and anti-TIGIT antibodies affect CD8+ cytotoxic T cells. In an initial experiment, mice were injected with a murine colorectal tumor cell line and then treated with anti-PD-1 and anti-TIGIT antibodies alone and in combination. When tumor volume was assessed on day 23, it was observed that while in mice given either anti-PD-1 or anti-TIGIT, some reduction in tumor volume was seen. It was more notably observed that combination treatment of anti-PD-1 and anti-TIGIT had the most effective therapeutic result with a significant reduction in tumor volume as compared to mice treated with a control antibody or either monotherapy alone.5

To further investigate the mechanisms through which anti-PD-1 and anti-TIGIT reduced tumor volume, and to address the necessity of a dual blockade, Banta et al. ran another set of experiments.6 This time, the previous experiment was repeated, but with the addition of CD226/- mice. Previously, it had been shown that PD-1 was involved in the regulation of CD28 and TIGIT was involved in the regulation of CD226.7,8 However, Banta et al. found in these experiments, that in the absence of CD226, the effects of both the anti-TIGIT and anti-PD-1 antibodies were reduced or lost completely. This suggests the convergence of these two pathways at the inhibition of the immunostimulatory molecule CD226.6 Taken together, the findings published by Banta et al. suggest that dual blockade of the PD-1 and TIGIT pathways could result in promising outcomes for certain cancer patients. This is just the beginning of a new line of research being done to discover safer, more effective alternatives to chemotherapy.

With this research and accompanying results, a few questions are brought to light. First, how might dual anti-PD-1 and anti-TIGIT
ti-TIGIT therapy work across various cancer types expressing various levels of different immunoregulators, and second, would genetic characterization of immune checkpoint inhibitors be required for effective treatment of each individual’s cancer? In the research by Banta et al., the effectiveness of these treatments was investigated with a PD-L1hi murine colorectal carcinoma cell line (CT26). While this work found that dual anti-PD-1 and anti-TIGIT antibody therapy was successful in those tumors, emerging research suggests that advanced genetic screening of the tumor is required to determine which cocktail of immunotherapies would be effective to avoid harm to unscreened patients. Currently, the FDA has only approved antibody treatments involving CTLA-4, PD-1, and PD-L1, however, new targets are in development.

Altogether, the poor outcome of current anti-cancer treatments, combined with the promising preliminary data on various ICB therapies, calls for an increased focus on the topic. The work done by Banta et al. sets the stage for promising advancements in the development of these immune checkpoint treatments.

References