GITR: A Target to Enhance Antitumor Immune Response in Cancer
The immune system plays a significant role in the recognition and destruction of cancer cells

The immune system plays a central role in host protection, guarding against both exogenous and endogenous threats, including the recognition of cancer cells and providing anti-tumor defenses. However, the immune system will inevitably lose the ability to identify and destroy nascent tumors, as tumors continually adapt in order to evade surveillance, recognition and destruction by the immune system. To that end, tumors that grow sufficiently to be detected have by some mechanisms escaped eradication by the immune system.
One critical component of the immunological response to cancer cells is dependent on a robust T effector cell response that is specific for tumor associated-antigens. Effective T cell activation, a consequence of both receptor-antigen-major histocompatibility complex (MHC) binding and engagement of co-stimulatory molecules, is required to drive a strong immune response. The glucocorticoid-induced tumor necrosis factor-related protein, or GITR, is a key modulator of T cell response, an important part of the anti-tumor activities of the immune system. Research to validate the role of GITR as an important co-stimulatory molecule that enhances anti-tumor actions of effector T cells is ongoing.
While the exact mechanisms by which tumors evade immune detection are not yet fully understood, there is abundant evidence that confers the importance of immune surveillance, and the need for therapeutic strategies to enhance host immune defenses for eradication of tumors. Despite ongoing surveillance by T cells and other components of the immune system, tumors develop and grow even in the presence of an intact immune system and eventually become clinically detectable.¹
The immune response to cancer cells can be inhibited or abrogated for a variety of reasons. For example, tumor antigens may not be properly detected, or may be inappropriately recognized as “self” by dendritic cells (DCs) and T cells, inhibiting production of a robust immune response. Certain interleukins and other molecules can inhibit T cell priming and activation, further diminishing the likelihood of effective response by the immune system. Furthermore, T cells may not localize to or properly infiltrate tumors effectively, and may be unavailable to provide cytotoxic antitumor effects. Suppressive factors within the tumor microenvironment can also inhibit effector cells that manage to access the tumor, additionally abrogating the immune response. The terminal consequence of these varied immune events is that host immune functions ultimately fail to detect and control tumor growth.
Approaches that modulate the immune system may improve the immune response to cancer

The cancer-immunity cycle illustrates the complex interactions that occur between the immune system and cancer that result in effective killing of cancer cells. To exploit the potential benefits of the immune response, an appreciation of the immune system is essential. Tumor antigens or neoantigens on tumor cells are released and subsequently taken up by DCs. These antigens are processed and presented to T cells on MHC I and II molecules, consequently leading to the priming and activation of the T cells. T cell immune responses are a result of a balance between stimulatory and inhibitory signals. The ratio of T effector cells to T regulatory cells is one of many factors that determines the outcome of the anti-tumor immune response.
In response to signaling through various molecules, activated effector T cells migrate to and subsequently infiltrate a tumor, where they bind specifically to tumor cells as T cell receptors recognize tumor antigens. These activated cytotoxic T effector cells kill the tumor cells to which they are bound, triggering the release of additional tumor cell antigens, thus further driving the cancer-immunity cycle.

Understanding the mechanisms by which tumor surveillance occurs, and how these mechanisms ultimately fail, may guide approaches to tumor immune therapy. Effective cancer immunotherapies act to help the immune system overcome the mechanisms of tumor evasion that impair the immune response. Thus, agents that act to promote ongoing immunity may hold promise in the management of cancer.
The success of immune checkpoint inhibitors has driven investigations for other agents that enhance the anti-tumor immune response. One avenue of exploration that may have value is the activation of co-stimulatory pathways. The tumor necrosis factor receptor superfamily, or TNFRsf, is involved in a host of critical functions that influence B and T cell development, survival, immune activation, as well as modulating the immune antitumor response, and act by stimulating activation and pro-inflammatory pathways. TNFRsf includes several molecules that are co-stimulatory proteins known to play key roles in immunomodulation. One TNFRsf member, GITR, is an important stimulatory protein that affects T cell activation.
GITR (CD357) is expressed at very low levels on resting CD4+ and CD8+ T cells, but it is up-regulated upon stimulation. However, in T regulatory cells (T regs) GITR is constitutively expressed. GITR is also present on DCs, monocytes, and natural killer cells. GITR ligand (GITRL) is a type 2 transmembrane protein, as is typical for most TNF ligand family members. GITRL is expressed at high levels on activated antigen presenting cells (APCs) and endothelial cells, and on activated T cells. Interactions between GITR on T cells and its ligand GITRL on APCs are bi-directional—both cell types are influenced by the interaction—ultimately resulting in T cell proliferation. Binding of GITR to GITRL triggers signaling which co-stimulates both CD8+ and CD4+ effector T cells, leading to enhanced T cell expansion and effector function, while suppressing the activity of T reg cells. GITR co-stimulation promotes the transition of anergic, hypoproliferative T cells to a hyperproliferative state. This may translate into markedly enhanced T cell activation, leading to a more effective anti-tumor immune response.

Preclinical data has shown that ligation of GITR modulates T regs, which causes a significant diminution in the accumulation of suppressive cells within the tumor microenvironment. This ultimately promotes higher local effector T cell—T reg ratios, which leads to improved antitumor cytotoxic T cell function.
The immune system serves to protect the host by recognizing and eliminating foreign and abnormal cells, yet it ultimately fails to effectively detect and destroy cancer cells. Tumors continually evolve and adapt in order to evade immune surveillance and destruction. The goal of immunotherapy in cancer is to assist the immune system to overcome the multiple mechanisms of evasion employed by cancer cells, permitting an effective host anti-tumor immune response leading to prolonged responses. The cancer-immunity cycle describes the mechanisms by which tumors and immune cells interact, and it highlights different points at which immuno-therapeutic approaches may be considered. GITR is a key stimulatory protein involved in the priming and activation of effector T cell responses.
GITR-GITRL interactions support effective anti-tumor immune responses, both by promoting expansion and activation of effector T cell populations and by suppressing T reg functions, which suppress immune activity. This critical step is vulnerable to pharmacologic interventions that may enhance the anti-tumor response. Modulation of co-stimulatory members of TNFRsf such as GITR represents a promising approach to immunotherapy and may allow for elucidation of mechanisms by which tumor-specific immune responses may be enhanced.⁴
References