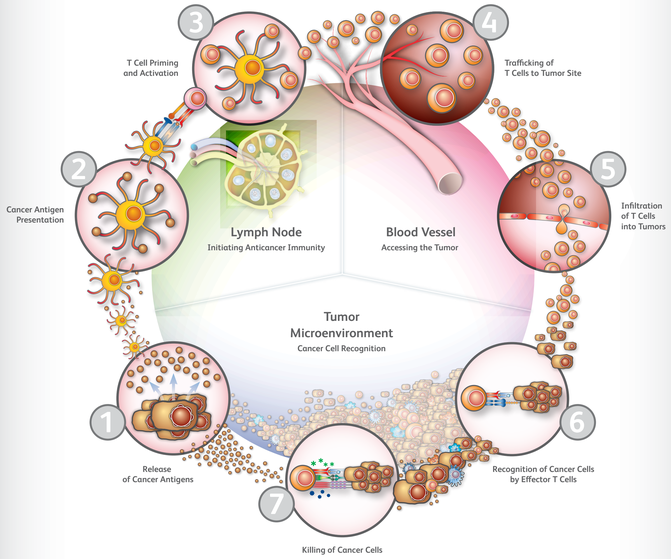
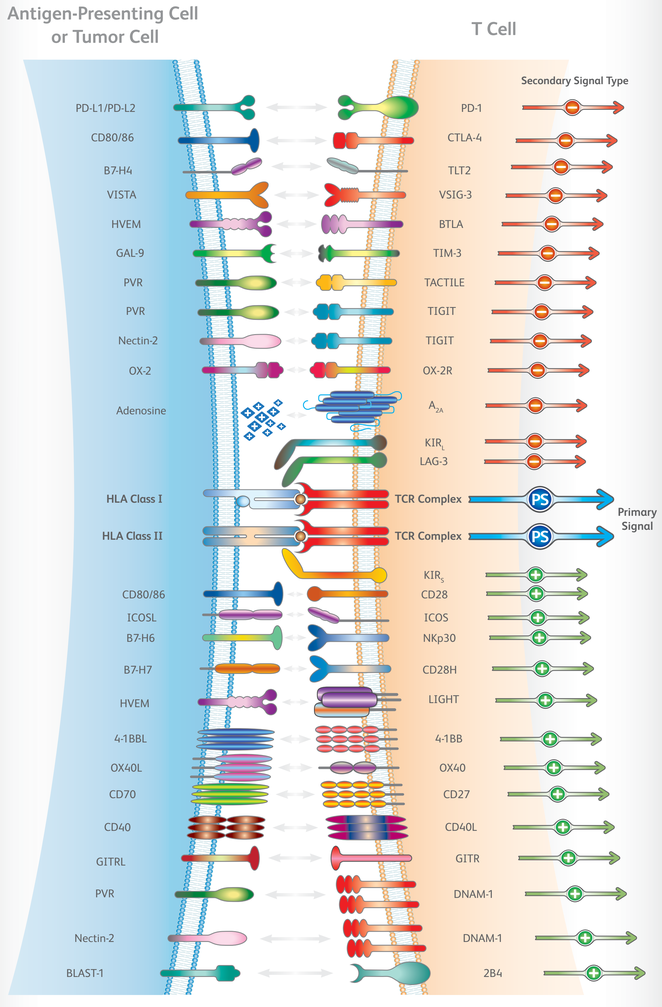
Cancer Immunotherapy

The Role of Immune Checkpoint Receptors in Cancer Immunity

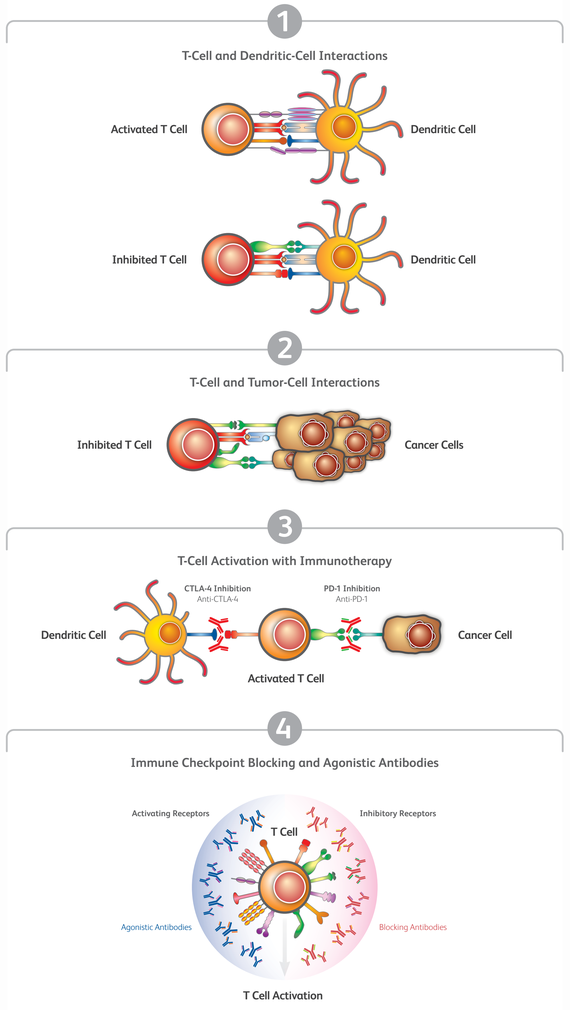
Cancer Immunity Cycle



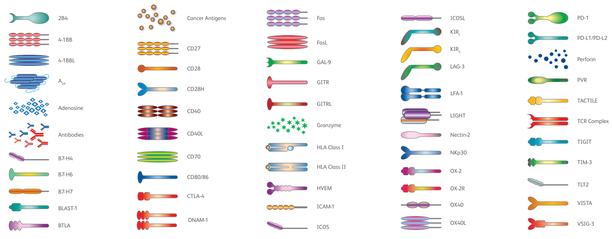
Immune Checkpoint Receptors



Cell Interactions & Immunotherapy



Legend:



The immune system plays a crucial role in protecting the body against cancer by recognizing and killing cells it perceives as foreign. Restoring the immune system's abilities to develop an antitumor immune response is the goal of many cancer immunotherapeutic strategies. Many strategies aim to block the mechanisms that prevent T cells from infiltrating the tumor microenvironment or generating an immune response. Other strategies try to stimulate an immune response that strengthens the detection and destruction of developing tumors and reduces the likelihood of continued tumor growth and metastases. The cancer immunity cycle depicts the cycle of T-cell activation and tumor killing along with steps where therapies can be employed to disrupt the immunosuppressive processes that promote tumor growth and increase the immune system's power to fight cancer.

Step 1: Release of Cancer Antigens

The cancer immunity cycle begins with the release of tumor antigens, including neoantigens, as a result of tumorigenesis. These antigens are recognized by the host immune system and are captured and processed by dendritic cells for antigen presentation. Additional immunogenic signals that induce immunity are required to initiate anticancer T-cell responses. These signals include proinflammatory cytokines and factors released by dying tumor cells. Therapeutic strategies here include immunotherapy, chemotherapy, radiation therapy, oncolytic virotherapy, bacterial therapy and targeted therapy.

Step 2: Cancer Antigen Presentation

Dendritic cells or other APCs capture antigens and present them on HLA class II molecules to $CD4^+$ T cells (helper T cells). Antigen-bearing dendritic cells can also cross-present cancer-associated antigens to $CD8^+$ cytotoxic T cells (CTLs) in a HLA-class-I-dependent manner. Therapeutic strategies here include therapeutic vaccines, dendritic cell vaccines, TNF-α, GM-CSF, anti-CD40 (agonist) and TLR agonists.

Step 3: T Cell Priming and Activation

Antigen presentation along with co-stimulatory signals, for example CD28, in the lymph node leads to priming and activation of effector T-cell responses against the cancer-specific antigens. This is a crucial step where the nature of the immune response is determined. The outcome of this stage is also influenced by the ratio of effector T cells versus regulatory T cells. Therapeutic strategies here include anti-CTLA-4, anti-CD137 (agonist), anti-OX40 (agonist), anti-CD27 (agonist), IL-2 and IL-12.

Step 4: Trafficking of T Cells to the Tumor Site

After clonal expansion, anticancer-specific effector T cells acquire the ability to traffic from the lymph node and enter the bloodstream to travel through the body to the tumor bed.

Step 5: Infiltration of T Cells into Tumors

The activated effector T cells infiltrate through blood vessel endothelial cells, through the tumor stroma (including the extracellular matrix, fibroblasts and other cells) and enter the tumor bed. Therapeutic strategies here include anti-VEGF, CXCR2 inhibition and CXCL12 inhibition.

Step 6: Recognition of Cancer Cells by T cells

T cell positioning and migration within the tumor site enable interactions of effector or memory T cells with tumor cells. The activated CTLs specifically recognize and bind to cancer cells in the tumor microenvironment through the interaction of the TCR and associated antigen bound to HLA I. Interaction between LFA-1 and ICAM-1 is also needed for firm adhesion to the cancer cell and proper orientation of cytolytic granules toward the cancer cell. Therapeutic strategies here include CAR T cells, bispecific monoclonal antibodies (BiTE®), CEA TCBs and ImmTAC® molecules.

Step 7: Killing of Cancer Cells

The final step involves killing of the target tumor cells by the activated CTLs. Killing of the tumor cells releases additional tumor-associated antigens and proinflammatory cytokines which starts the cycle again to help increase the depth of the immune response. Therapeutic strategies here aim to revert T-cell exhaustion state and include anti-PD-1, anti-PD-L1, inflammasome agonists and IDO inhibitors.

The human immune system has an important role in fighting foreign pathogens, protecting against diseases, clearing the body's own dying cells and recognizing and eliminating cancer cells. In cases of both blood cancers and solid tumor cancers, the ubiquitous presence of antigens that are associated with these pathological states can result in over-stimulation of the immune system, leading to T-cell exhaustion. An over-stimulated immune system can eventually break tolerance to self-antigens, leading to autoimmune conditions. To mitigate this process, the immune system has evolved a series of negative regulators, or checkpoint molecules, in the form of a family of receptors and signaling pathways. These checkpoint receptors effectively inhibit an immune response and prevent autoimmune disease. These molecules are collectively known as immune checkpoint receptors.

Immune checkpoint receptors are critical regulators of immune responses. They control the initiation of a productive immune response and also act during later phases of the immune response to prevent excessive cell activation that could lead to inflammatory autoimmune processes and mistakenly destroying healthy cells. These co-inhibitory and co-stimulatory immune checkpoint receptors control full T-cell activation and effector functions. During the course of an antitumor immune response, tumor immunogenicity changes and additionally tumor cells may exploit immune checkpoints to favor tumor growth. As a result, malignant cells can escape immune surveillance and elimination. Blocking inhibitory immune checkpoint receptors, such as CTLA-4 or PD-1, in cancer enables tumor-reactive T cells to overcome regulatory mechanisms and elicit a robust antitumor response with the recognition of tumor antigens and tumor regression. In autoimmune diseases, the converse strategy of activating these receptors may alleviate inflammation.

With the probability of 1 in 4 people being diagnosed with cancer in their lifetime, finding new treatment strategies for cancer has become a challenging goal for researchers. Stimulating the inherent ability of the immune system to attack and destroy cancer cells established an entirely new principle for cancer therapy and led to new scientific advancements. The breakthrough discovery of cancer therapy through the inhibition of negative immune checkpoint regulators was selected for the 2018 Nobel Prize in Physiology or Medicine and awarded jointly to James P. Allison and Tasuku Honjo. Both researchers studied proteins that had the potential to release the brakes on the immune system and unleash the power of immune cells to attack tumors.

These discoveries have led to the clinical development of highly effective immunotherapies for cancer and inspired efforts to combine differing immune-checkpoint-receptor strategies to attack tumor cells more efficiently. An increasing number of checkpoint therapy trials are currently underway against several cancer types and new checkpoint proteins are being tested as potential new targets in the design of next-generation immunotherapies.

1. T-Cell and Dendritic-Cell Interactions

Immune checkpoint receptors are upregulated on the surface of T cells upon activation. Effective activation of $CD4^+$ T cells is driven initially from interactions with mature dendritic cells, which present tumor-associated antigens in a HLA-class-II-dependent manner and require the interaction of CD80 with CD28 on the T cell.

Immune-checkpoint-receptor interactions, such as ICOS/ICOSL or OX40/OX40L, help to prime and activate T cells, while PD-1/PD-L1 or CTLA-4/CD80 interactions inhibit T-cell effector functions, which can help balance the immune response and prevent the onset of chronic inflammation and autoimmune processes.

2. T-Cell and Tumor-Cell Interactions

Tumor cells within the tumor microenvironment can exploit the immune checkpoint pathways and inhibit the antitumor response, leading to cancer progression. This is done by over-expressing inhibitory immune checkpoint receptors, such as PD-L1 and GAL-9 that bind to inhibitory PD-1 and TIM-3, respectively, on the surface of the T cells.

3. T Cell-Activation with Immunotherapy

CTLA-4 is induced and expressed on activated T cells at the time of their initial response to antigens in the lymph node. To maintain immunologic balance, CTLA-4 downregulates the function of activated T cells through the interaction with CD80. PD-1 is expressed on activated T cells in the lymph node (early stage) and tumors (late stage) in the tumor microenvironment. In both early and late stages, PD-1 maintains immunologic balance by downregulating the function of activated T cells through engagement with PD-L1 or PD-L2.

Tumors may induce immune tolerance through the inhibitory signaling of CTLA-4 or PD-1, which can enhance the survival of the cancer cells. The goal of anti-CTLA-4 or anti-PD-1 immunotherapy is to release the brakes on immune cells by blocking the negative signaling and restoring the immune cell's ability to kill the cancer cells.

4. Immune Checkpoint Blocking and Agonist Antibodies

Agonistic antibodies directed against activating co-stimulatory receptors and blocking antibodies against co-inhibitory receptors may enhance T-cell stimulation to promote the killing of cancer cells. Several FDA-approved therapeutic antibodies have been developed against these receptors, such as anti-CTLA-4 and anti-PD-1 antibodies, which have been successfully used for treatment of metastatic melanoma and other cancer types.

Abbreviations:

A_{2A}, adenosine receptor A_{2A}; **APC**, antigen-presenting cell; **BiTE®**, Bi-specific T-cell engagers; **Blast-1**, B-lymphocyte activation marker, CD48; **BTLA**, B and T lymphocyte attenuator; **CAR**, chimeric antigen receptor; **CD40L**, CD40 ligand, CD154; **CEA**, carcinoembryonic antigen; **CTL**, cytotoxic T lymphocyte; **CTLA-4**, cytotoxic T-lymphocyte-associated protein 4, CD152; **CXCR2**, C-X-C motif chemokine receptor 2; **CXCL12**, C-X-C motif chemokine ligand 12; **DNAM-1**, DNAX accessory molecule-1, CD226; **Fas**, first apoptosis signal receptor, CD95; **FasL**, Fas ligand, CD95L; **FDA**, Food and Drug Administration; **GAL-9**, galectin 9; **GITR**, glucocorticoid-induced TNFR family-related gene; **GITRL**, glucocorticoid-induced TNFR family-related gene ligand; **GM-CSF**, granulocyte-macrophage colony-stimulating factor; **HLA**, human leukocyte antigen; **HVEM**, herpesvirus entry mediator; **ICAM-1**, intercellular adhesion molecule 1; **ICOS**, inducible T cell co-stimulator; **ICOSL**, inducible T cell co-stimulator ligand; **IDO**, indoleamine 2,3-dioxygenase; **IL**, interleukin; **ImmTAC®**, immune-mobilising monoclonal TCRs against cancer; **KIR_L**, killer-cell immunoglobulin-like receptor, long-tailed; **KIR_S**, killer-cell immunoglobulin-like receptor, short-tailed; **LAG-3**, lymphocyte-activation gene 3; **LIGHT**, homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes (or TNFSF14, tumor necrosis factor superfamily member 14), CD258; **LFA-1**, lymphocyte function-associated antigen 1; **Nectin-2**, nectin cell adhesion molecule 2, CD112; **NKp30**, natural cytotoxicity receptor, CD337; **OX-2**, 2-(beta-D-Glucopyranosyl)-5-methyl-1,3,4-oxadiazole, oxalate ion; **OX-2R**, orexin receptor type 2; **PD-1**, programmed cell death protein 1, CD279; **PD-L1**, programmed death-ligand 1, CD274; **PD-L2**, programmed death-ligand 2, CD273; **PVR**, poliovirus receptor, CD155; **TACTILE**, T cell activation, increased late expression, CD96; **TCB**, T-cell bi-specific antibody; **TCR**, T-cell receptor (alpha or beta); **TIGIT**, T cell immunoreceptor with Ig and ITIM domains; **TIM-3**, T cell immunoglobulin and mucin domain-3; **TLR**, toll-like receptor; **TLT2**, Trem-like transcript 2 protein; **TNF-α**, tumor necrosis factor alpha; **VEGF**, vascular endothelial growth factor; **VISTA**, V-domain Ig suppressor of T-cell activation; **VSIG-3**, V-set and Ig domain-containing protein 3 (or IGSF11, immunoglobulin superfamily member 11).