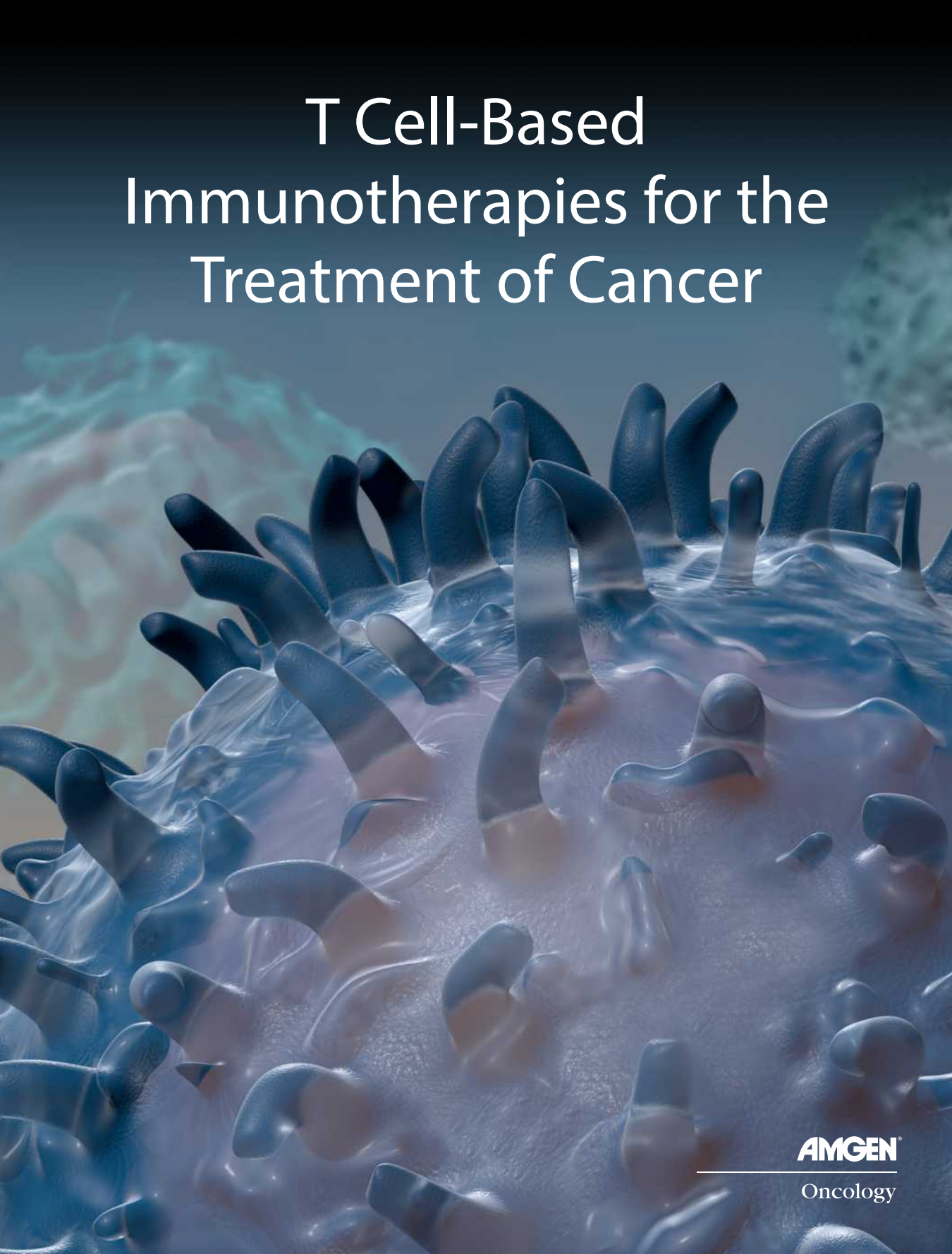
T Cell-Based Immunotherapies for the Treatment of Cancer



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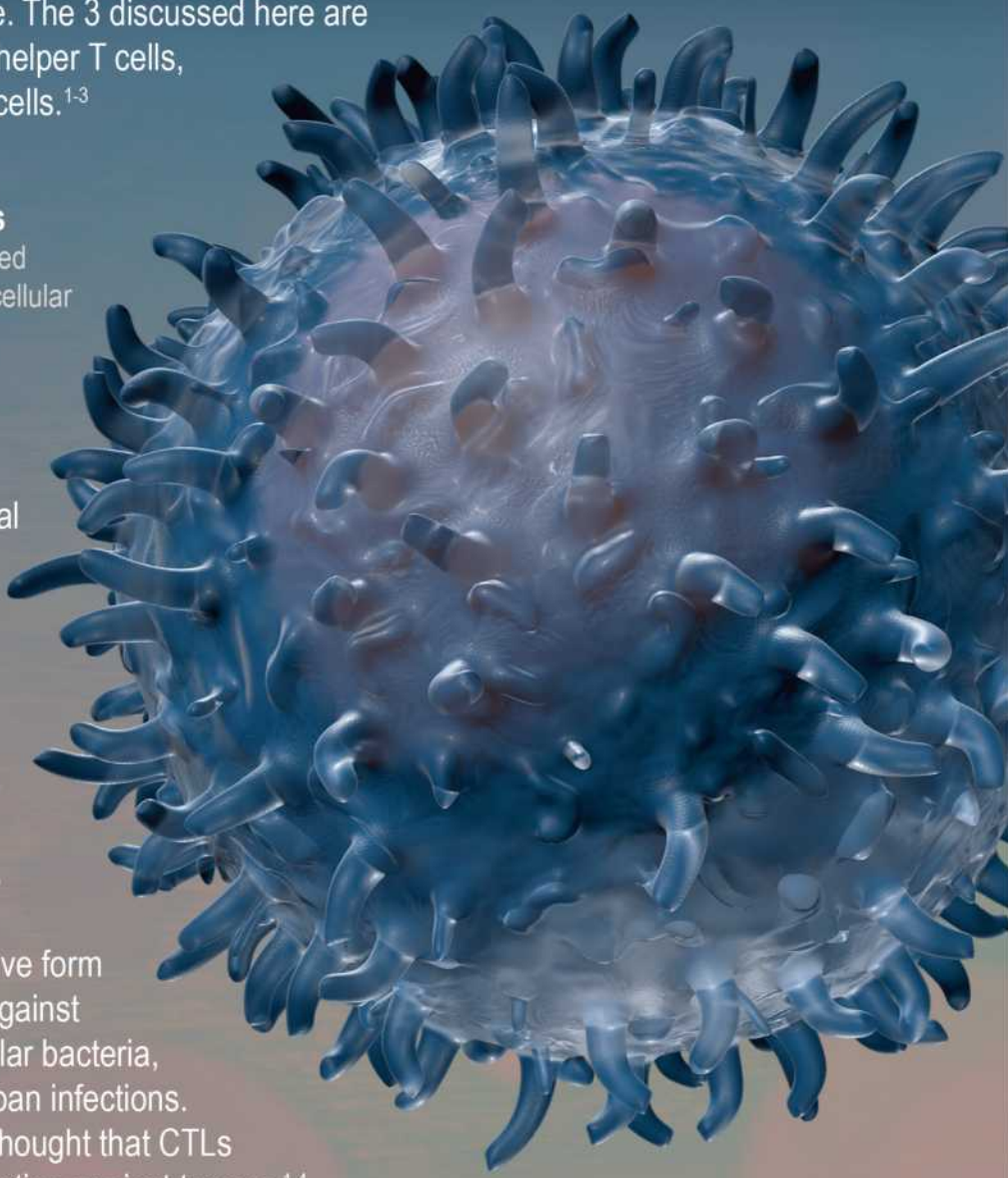
Overview of T Cells

T cells are components of the immune system that arise from the bone marrow and migrate to the thymus for maturation. Mature T cells that leave the thymus are considered naive until they are exposed to an antigen. The immune system has several types of T cells, which are grouped into various subsets based on their effector functions and molecular phenotype. Each of these subsets promotes a different type of immune response. The 3 discussed here are cytotoxic T cells, helper T cells, and regulatory T cells.[1-3]

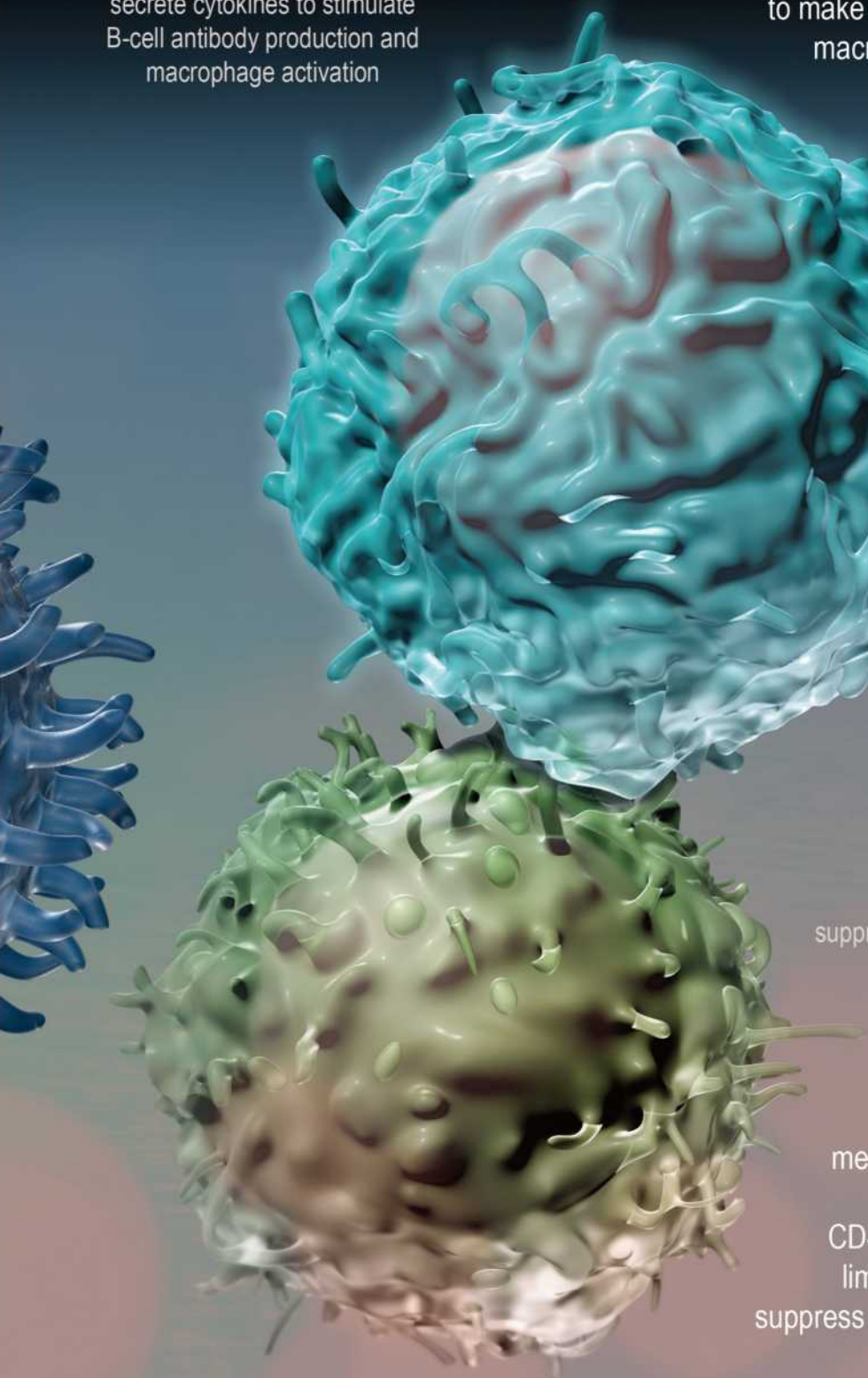


Cytotoxic T cells
eliminate cells infected with viruses or intracellular pathogens

Cytotoxic T lymphocytes, or CTLs, are principal components of immune function. CTLs are highly specific and potent effector cells that mediate directed lysis of target cells. CTLs represent a particularly effective form of host defense against viruses, intracellular bacteria, and some protozoan infections. Additionally, it is thought that CTLs can provide protection against tumors.[1-4]

Helper T cells
secrete cytokines to stimulate B-cell antibody production and macrophage activation

Helper T cells stimulate B cells to make antibodies, activate macrophages to destroy microbes, and help activate CTLs to eliminate infected cells.[2,3,5]



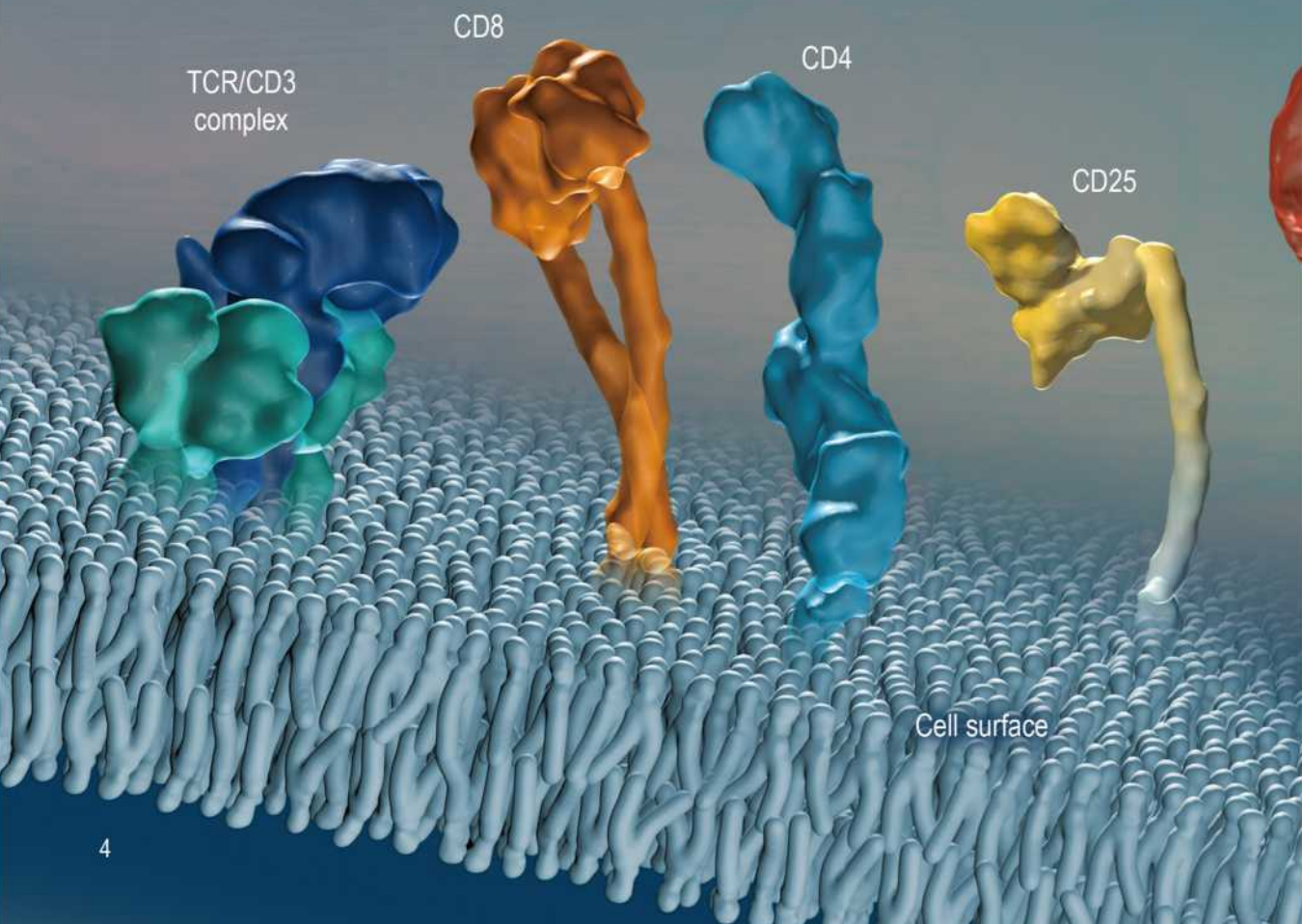
Regulatory T cells
suppress other lymphocytes and help regulate immune responses

Tolerance is a principal mechanism of immune escape whereby $CD4^+$ T regulatory cells limit inflammation and suppress immune response.[2]

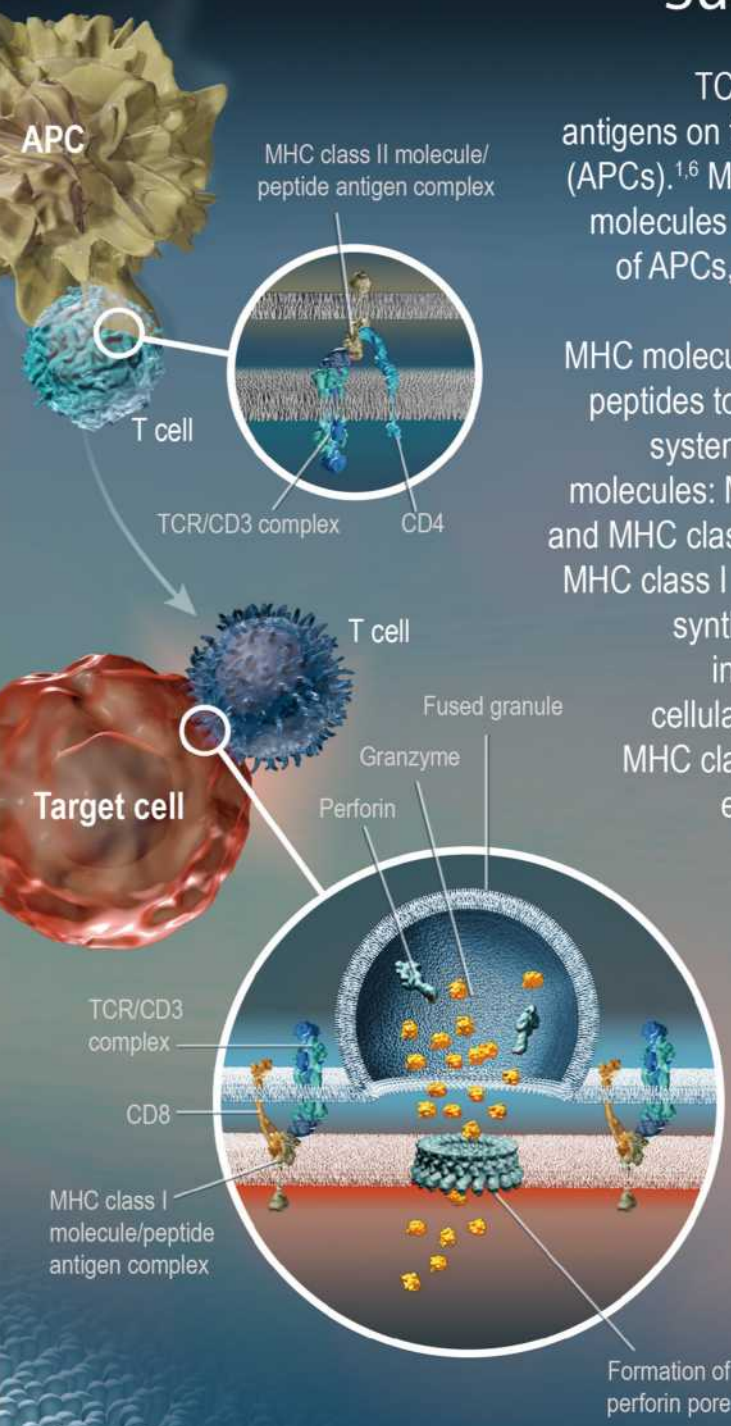
Features of the 3 Types of T Cells

T cells are distinguished by the proteins expressed on their cell surface.[2] The T-cell receptor (TCR) and CD3 protein complex are expressed on all T cells and influence antigen recognition and signaling. CD8 and CD4 are coreceptor proteins expressed on cytotoxic and helper T cells, respectively. Regulatory T cells express both CD4 and CD25.[2]

In the presence of pathogens, viruses, and other foreign bodies, T cells are activated to perform their respective functions. $CD8^+$ cytotoxic T cells eliminate infected cells. $CD4^+$ helper cells recruit and activate other immune cells such as B cells, which produce antibodies that help mount an immune response to the infection. $CD4^+/CD25^+$ regulatory T cells suppress the immune response after the pathogen has been destroyed.[2]



T Cells Recognize Antigens on the Surface of Target Cells



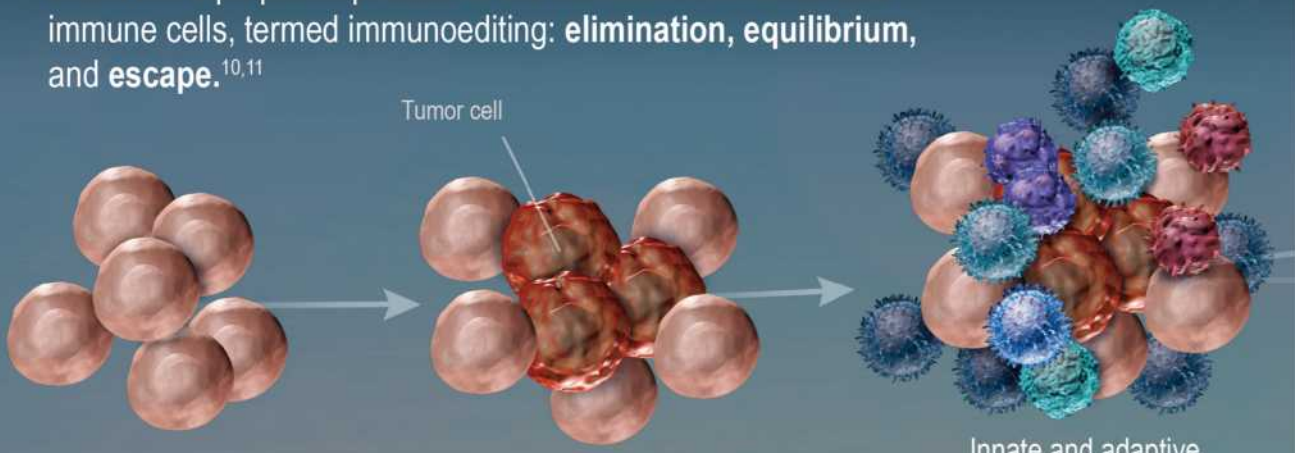
TCRs on the surface of T cells recognize antigens on the surface of antigen-presenting cells (APCs).[1,6] Major histocompatibility complex (MHC) molecules deliver foreign antigens to the surface of APCs, which are then recognized by TCRs.[1]

MHC molecules are able to present a vast array of peptides to T cells, playing a vital role in immune system functions. There are 2 types of MHC molecules: MHC class I, which interact with CTLs, and MHC class II, which interact with helper T cells. MHC class I presents peptides from endogenously synthesized proteins, allowing detection of intracellular pathogens and detection of cellular alterations indicative of cancer cells. MHC class II molecules present peptides from exogenously derived proteins, allowing for detection of threats such as extracellular pathogens.[1-3]

An immunological synapse is formed after the TCR/MHC-antigen complex and cell-adhesion interactions have been established.[6-8] The formation of the immunological synapse allows for T cell-mediated lysis via granule-dependent exocytosis.[8,9]

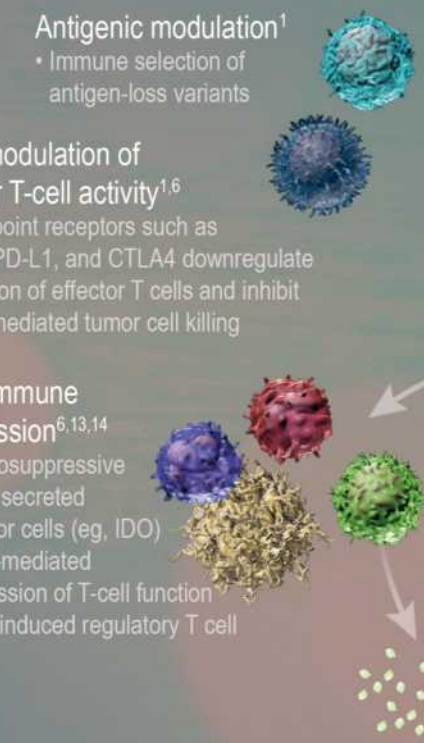
Tumor Cells Are Often Recognized and Eliminated Through T Cell-Mediated Immunosurveillance

There are 3 proposed phases for the interactions of tumor and immune cells, termed immunoediting: **elimination, equilibrium,** and **escape.**[10,11]



Multiple Pathways Allow Tumor Cells to Escape T-Cell Surveillance

The tumor microenvironment has multiple pathways through which cancer cells may evade the immune system.[1] Successful immunotherapeutic approaches have targeted the proteins involved in these pathways of immune escape. The opportunity exists to further enhance clinical activity through novel combinations of immunotherapies with different targets and/or mechanisms of action.[12]



Antigenic modulation[1]
- Immune selection of antigen-loss variants

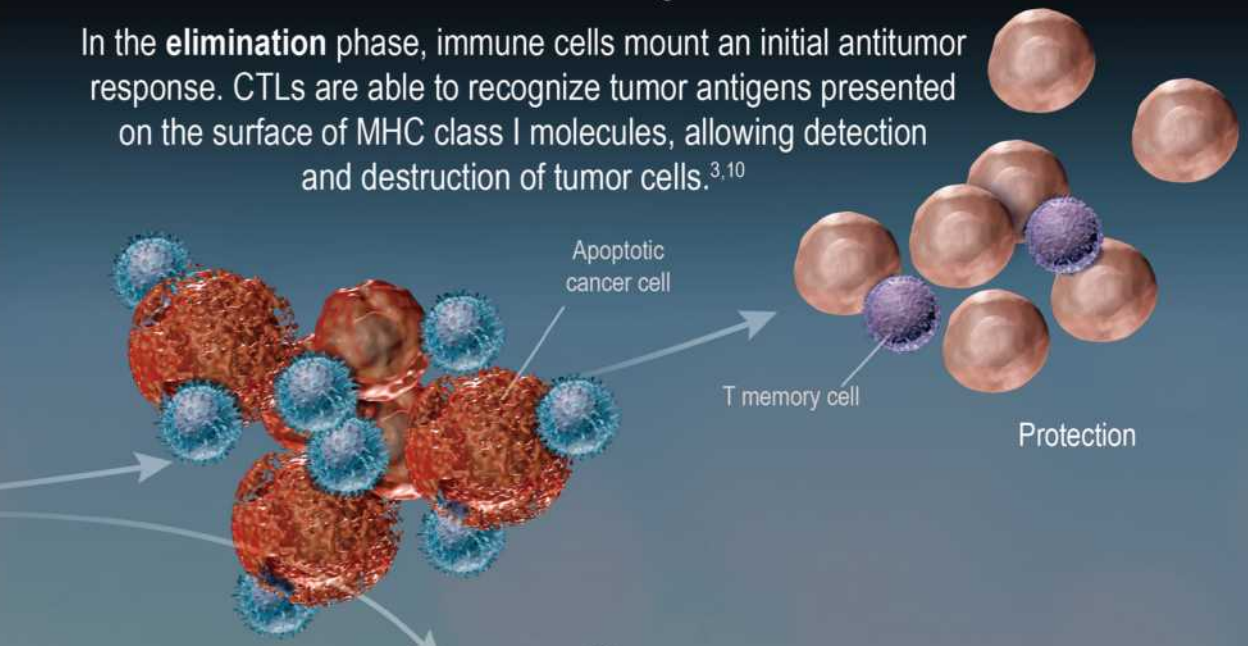
Downmodulation of effector T-cell activity[1,6]
- Checkpoint receptors such as PD-1, PD-L1, and CTLA4 downregulate activation of effector T cells and inhibit T cell-mediated tumor cell killing

Local immune suppression[6,13,14]
- Immunosuppressive factors secreted by tumor cells (eg, IDO)
- MDSC-mediated suppression of T-cell function
- Tumor-induced regulatory T cell

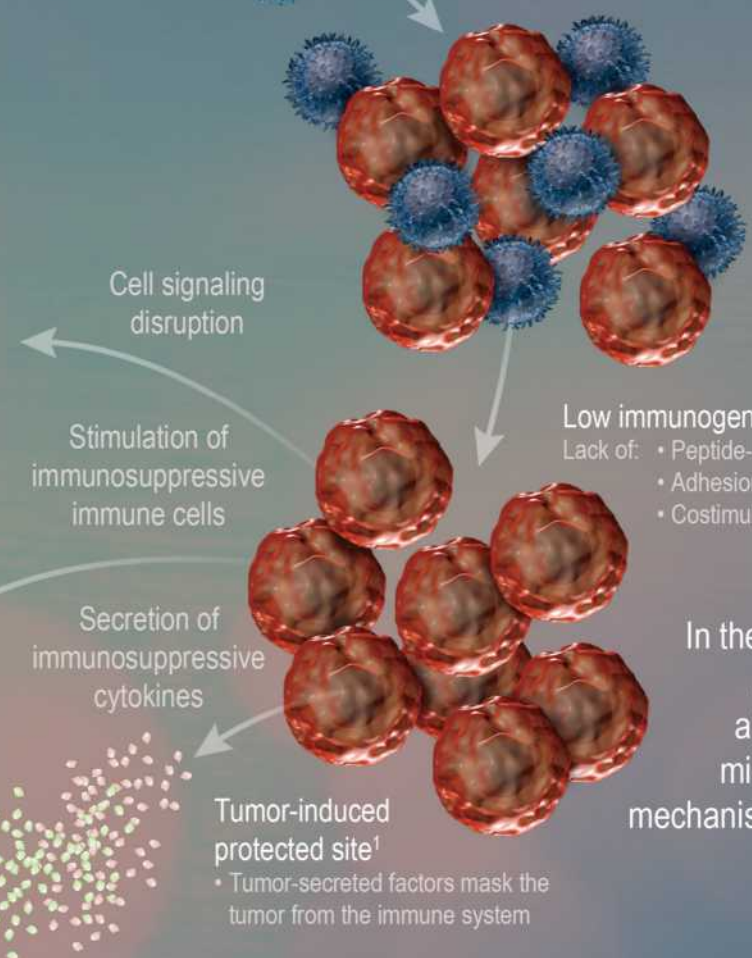
CTLA4, cytotoxic T-lymphocyte associated protein 4; IDO, indoleamine-2,3-dioxygenase; MDSC, myeloid-derived suppressor cell; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Cancer immunoediting

In the **elimination** phase, immune cells mount an initial antitumor response. CTLs are able to recognize tumor antigens presented on the surface of MHC class I molecules, allowing detection and destruction of tumor cells.[3,10]



Tumor cells that survive elimination enter the **equilibrium** phase where the immune system prevents tumor growth. However, some tumor cells can resist, avoid, or suppress the antitumor immune response so that they are no longer recognized by the immune system.[10]



Low immunogenicity[1]
Lack of:
- Peptide-MHC ligand
- Adhesion molecules
- Costimulatory molecules

In the **escape** phase, tumor cells emerge as progressive disease. Tumors can also establish an immunosuppressive microenvironment and acquire evasive mechanisms to escape the immune system.[10]

Tumor-induced protected site[1]
- Tumor-secreted factors mask the tumor from the immune system

T Cell-Based Approaches in Cancer

Several anticancer therapeutic strategies rely on the cytotoxic potential of T cells.

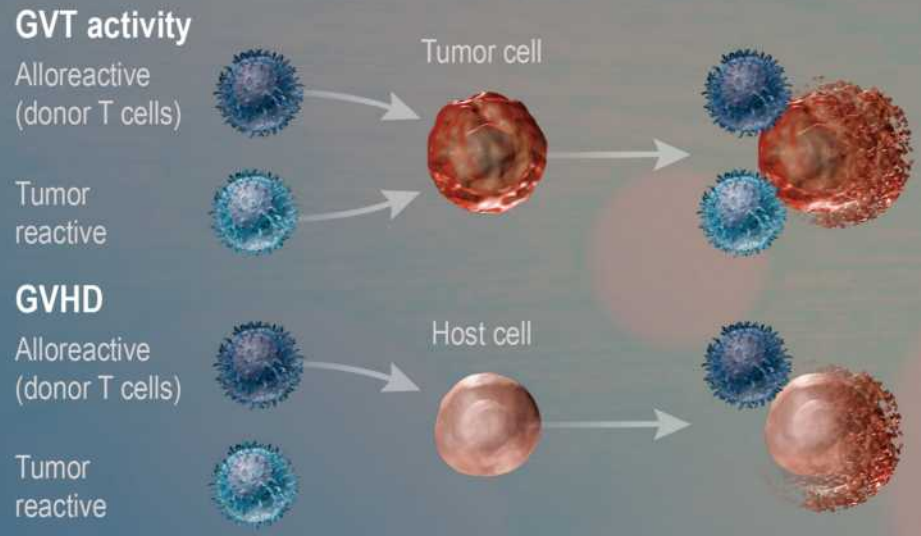
1957

Allogenic hematopoietic stem cell transplant (HSCT)

- Transplantation of bone marrow cells and peripheral blood stem cells[15]
- Tumor cells are eliminated through chemotherapy and graft-versus-tumor (GVT) effect[15]
- The first allogeneic HSCT was performed in 1957[16]

This approach involves transplantation of bone marrow cells and peripheral blood stem cells.[15] In allogeneic HSCT, tumor cells are eliminated through chemotherapy and the GVT effect.[15,17-19] The donor T cells recognize minor histocompatibility antigens.[15]

Allogeneic HSCT does have some limitations such as graft-versus-host disease (GVHD), which increases nonrelapse mortality.[15,18,19] The need for immune suppression also increases the risk of complications.[15]



Antibody-based targeted therapies

- Antibodies targeting checkpoint proteins such as CTLA-4, PD-1, and PD-L1 have resulted in the reactivation of T cell-mediated tumor cell killing[20]
- The first immune checkpoint inhibitor was approved in 2011[20]

Adoptive cell therapy

- T cells are isolated from the patient, manipulated ex vivo, and then infused into the patient[23]
- Autologous tumor-infiltrating lymphocytes were first used in melanoma in 1988[23]
- The first chimeric antigen T-cell (CAR T) therapy was approved in 2017[24]

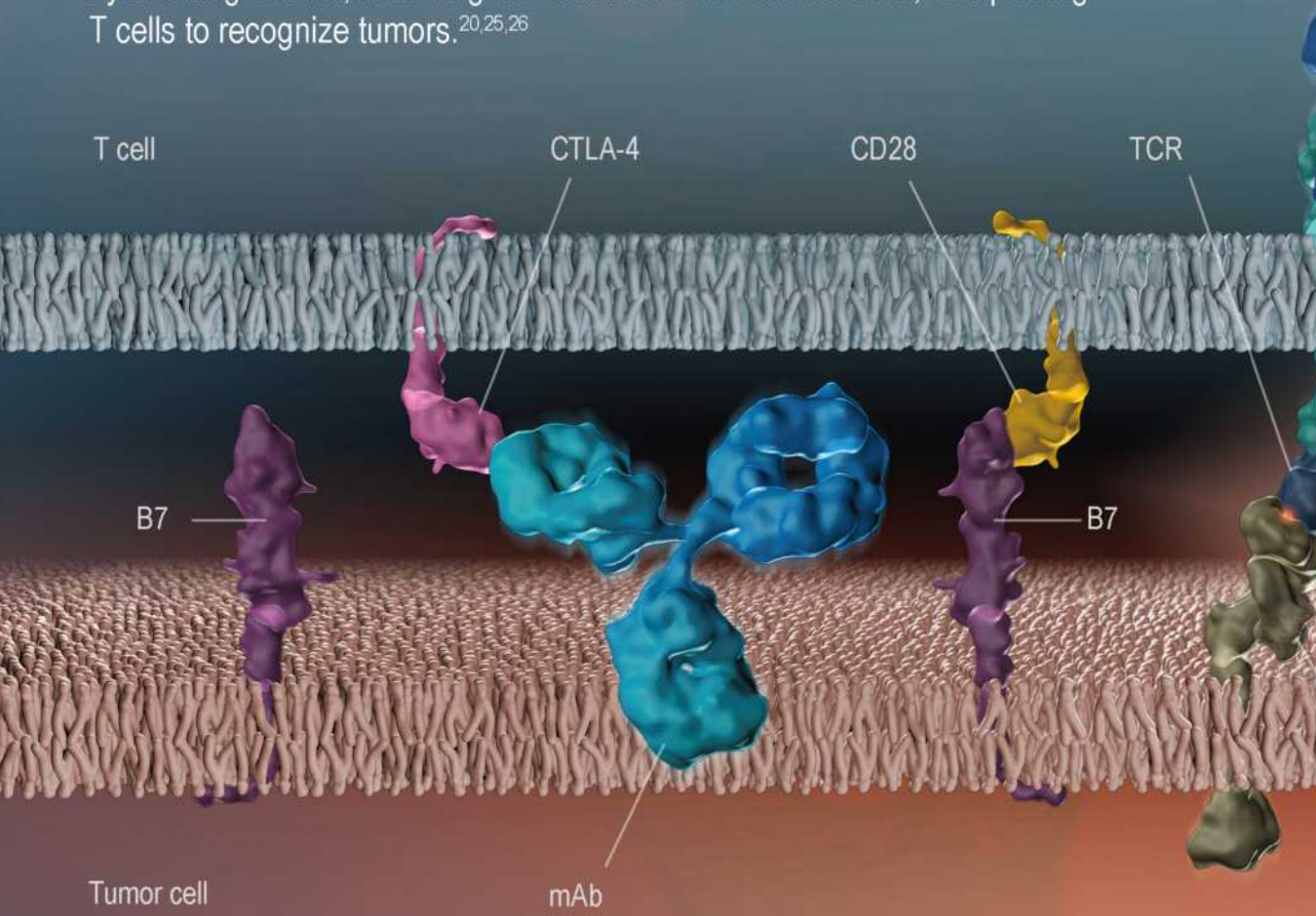
Bispecific T cell engagers (BiTEs®)

- Antibody constructs that redirect T cells to target cancer cells[21]
- BiTEs can be targeted against a variety of tumor antigens[21]
- The first BiTE targeted the CD19 antigen and was approved in 2014[22]

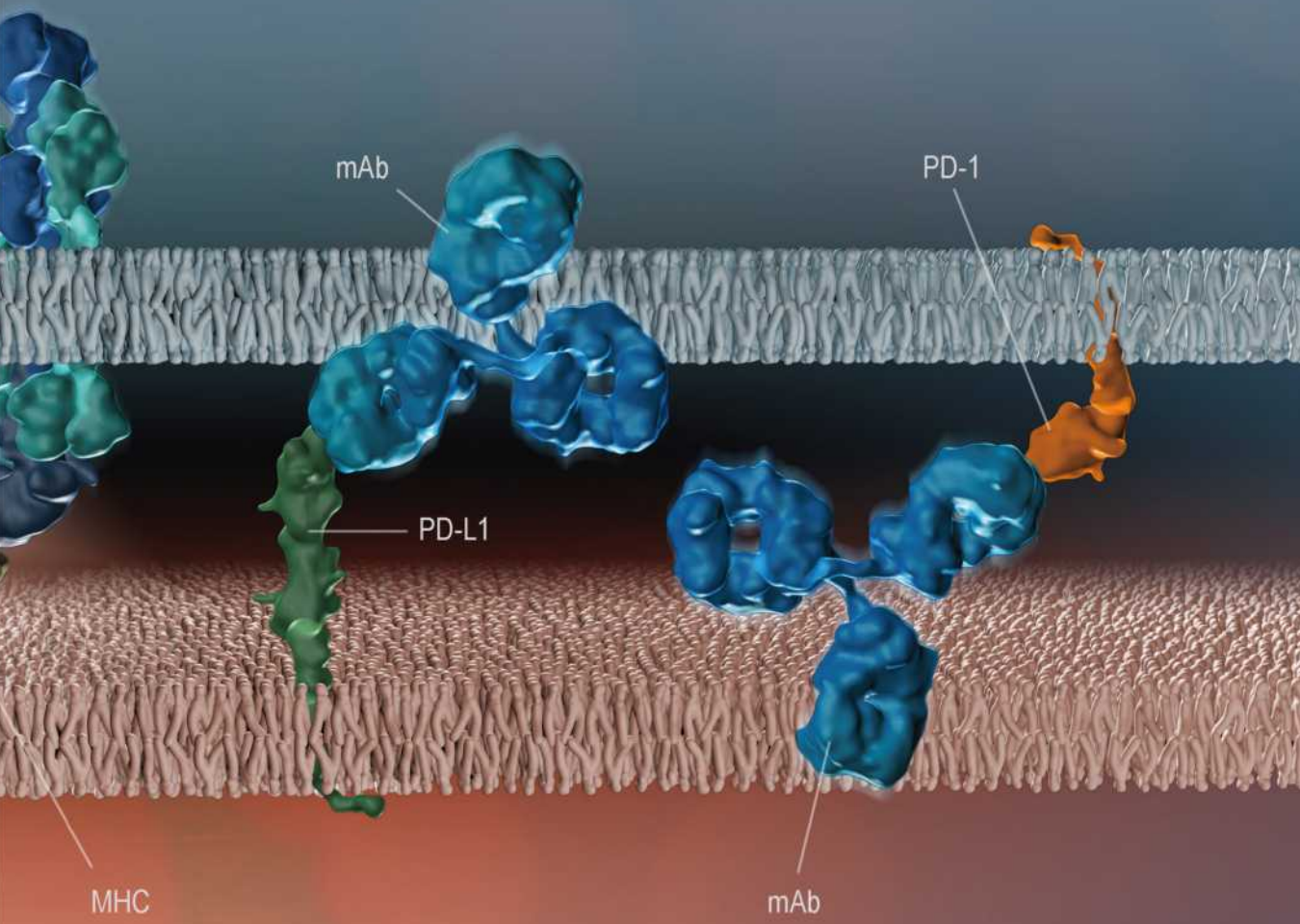
Antibodies Targeting Checkpoint Proteins

Under normal conditions, checkpoint receptors on the surface of T cells help to regulate the immune response and maintain homeostasis.[20,25,26] By binding to their ligands on other cells, checkpoint receptors help T cells distinguish between self and foreign cells and prevent damage to normal cells. However, tumor cells can take advantage of these checkpoints and evade immune detection by passing as normal cells. Inhibiting checkpoint proteins that negatively regulate the immune system can help to unmask the cancer cells.[20,26,27]

The checkpoint receptor CTLA4 suppresses T-cell activity by counteracting the T-cell costimulatory receptor CD28. Anti-CTLA4 mAbs augment T-cell activity by blocking CTLA4, removing the inhibition of T-cell activation, and priming T cells to recognize tumors.[20,25,26]



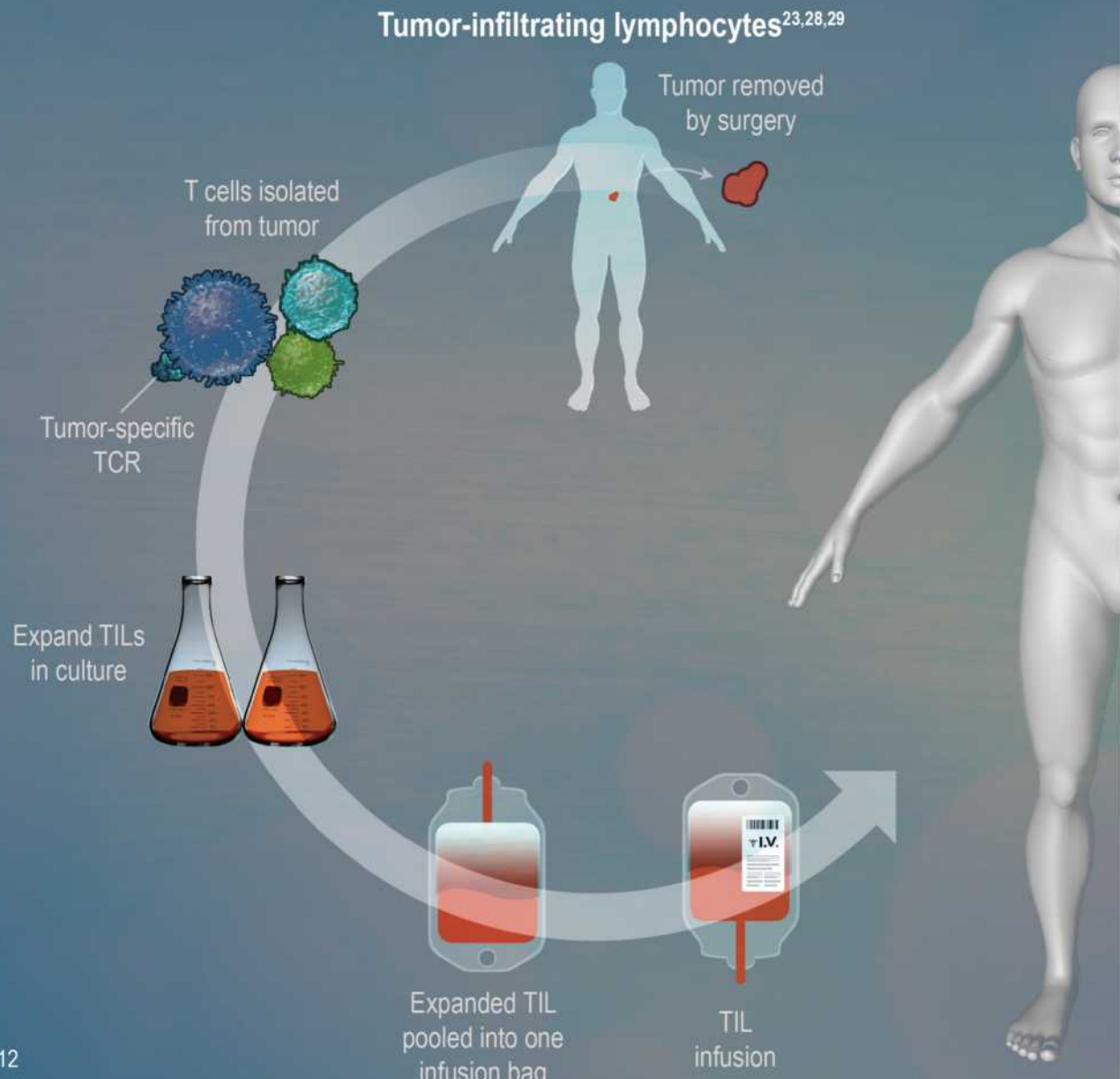
PD-1 is another checkpoint receptor that functions by inhibiting kinases involved in effector T-cell activation. Monoclonal antibodies targeting PD-1 and its ligand PD-L1 promote T-cell activation and enhance the ability of T cells to kill tumor cells.[20,25]



mAb, monoclonal antibody.

Adoptive Cell Therapy May Use Endogenous or Engineered Antigen Receptors

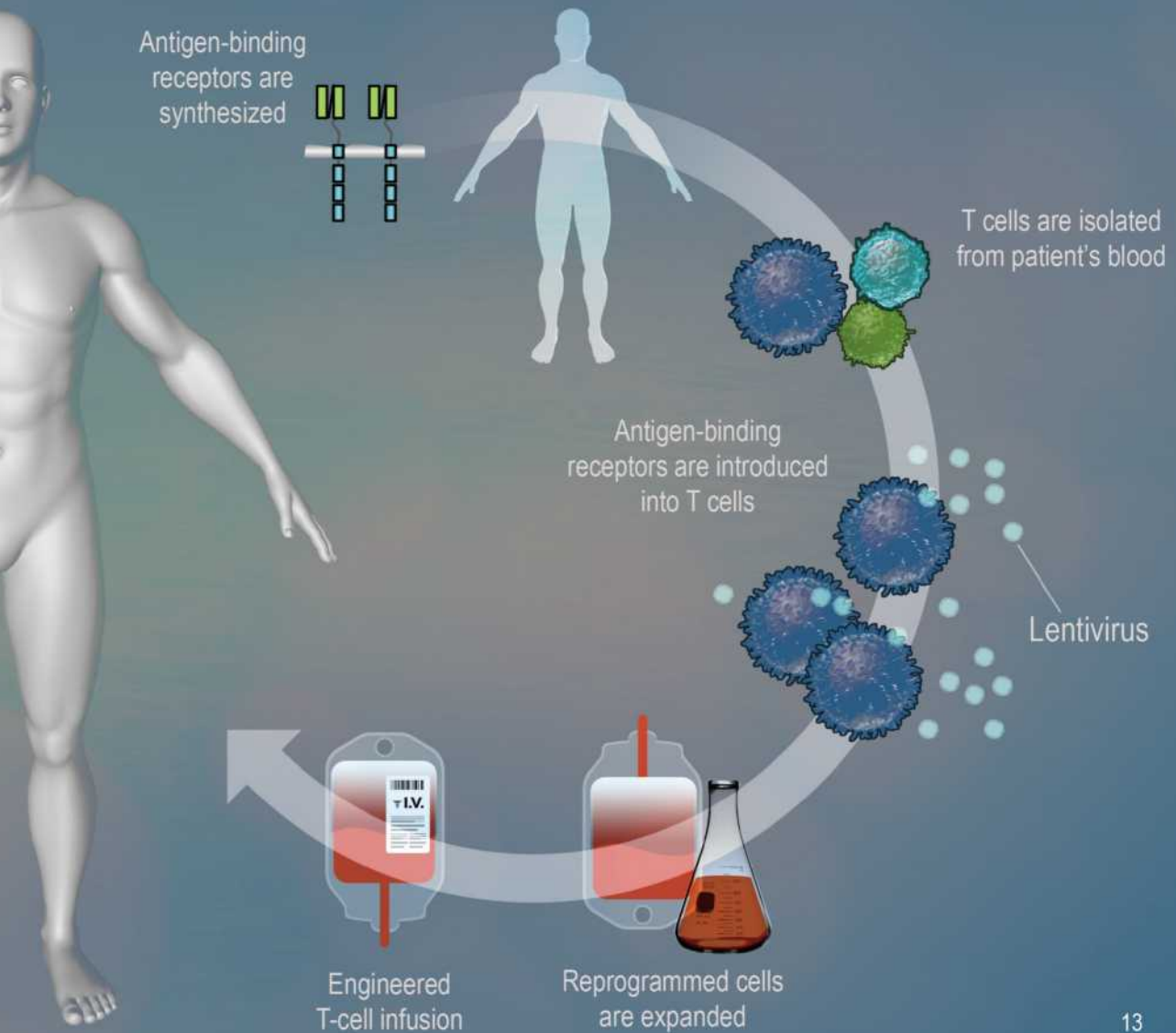
Treatment with tumor-infiltrating lymphocytes (TILs) involves isolating a patient's own white blood cells from tumor tissue. The isolated white blood cells are grown to large numbers. The expanded lymphocytes are then infused back into the patient, where they induce lysis of tumor cells and tumor regression.[23,28,29]



In the approach with CAR T cells, patients' T cells are isolated from their blood and genetically engineered with lentiviral vectors or DNA constructs that cause T cells to produce cell surface proteins targeted to recognize specific tumor antigens. The reprogrammed T cells are expanded to large numbers and infused into patients, where they target and kill tumor cells.[30-32]

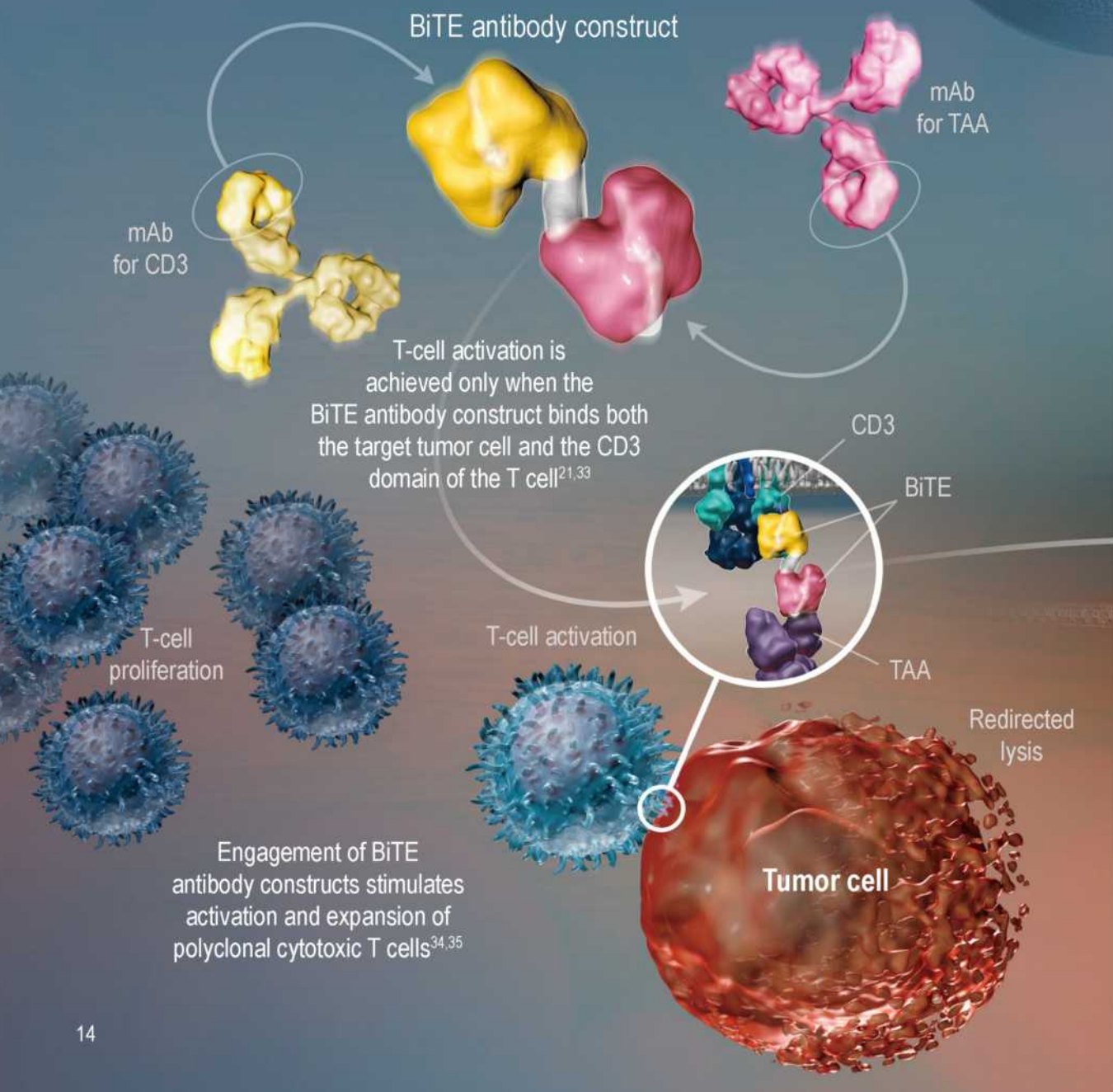
With both approaches, patients will typically receive lymphodepleting chemotherapy before infusion of the T cells.[32]

Engineered T cells (eg, CAR T cells)[30,31]



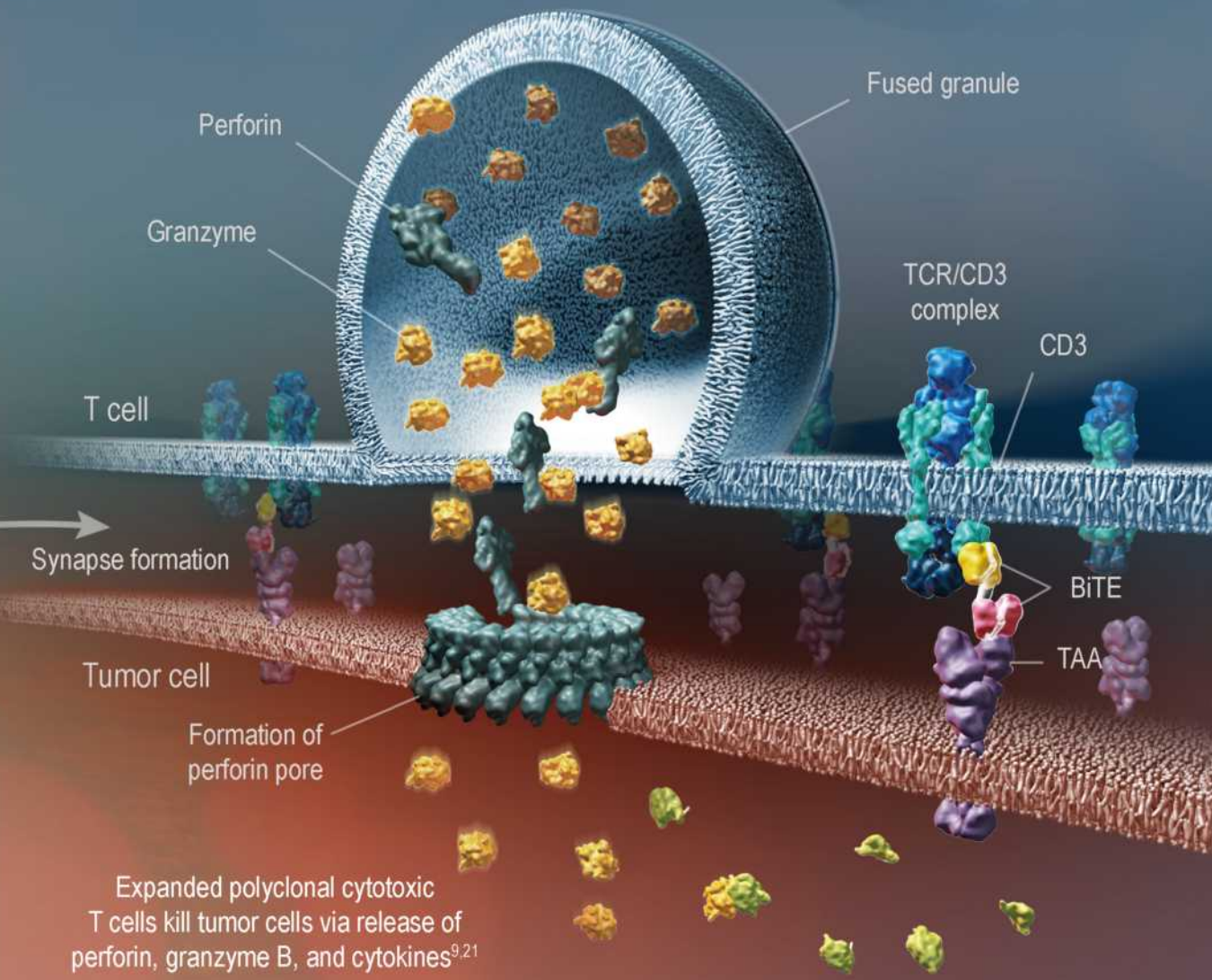
BiTE® Antibody Constructs

BiTE (bispecific T-cell engager) antibody constructs are generated by genetically linking minimal binding domains of mAbs that bind CD3 on T cells and surface antigens on target cancer cells.[21] As designed, one arm of the BiTE binds to the T cell, while the other binds to the target cell. Thus, the BiTE engages the T cell and creates a cytolytic synapse with the target cell, allowing for T cell-mediated killing through the release of pore-forming perforin, cytolytic granzymes, and cytokines.[9,21]



BiTE Antibody Constructs Harness the Cytotoxic Nature of T Cells

BiTEs use the immune system to fight cancer by connecting T cells to tumor cells, resulting in T-cell activation and targeted cell death.[9,21]



Expanded polyclonal cytotoxic T cells kill tumor cells via release of perforin, granzyme B, and cytokines[9,21]

TAA, tumor-associated antigen.

T cells have an innate ability to target tumor cells, and evidence supports a role for immunosurveillance in tumor targeting. T cells are pivotal in the recognition of tumor-associated antigens expressed by tumor cells. T cells are also involved in tumor cell infiltration.

However, tumor cells can escape immunosurveillance through several mechanisms, including antigen downregulation, T-cell dysregulation, and disruption of inhibitory pathways.

Several immunotherapy strategies aim to prevent tumor evasion by harnessing the innate ability of T cells to regulate tumor cells. Treatment with TILs and CAR T cells involves modification of the T cell population to more effectively target tumor cells. The BiTE® antibody constructs are designed to bridge $CD3^+$ cytotoxic T cells to antigens expressed on the surface of tumor cells.

Glossary

- **Antigen:** toxin or foreign substance that induces an immune response in the body
- **Cytokine:** protein released by certain immune cells that can trigger inflammation or response to infections
- **Immunogenicity:** the ability to provoke an immune response
- **Lymphocyte:** white blood cells responsible for immune responses
- **Pathogen:** foreign agent or microorganism that causes infection or disease
- **Tumor microenvironment:** the cellular environment in which the tumor exists, including the tumor cells, stromal cells, immune cells, fibroblasts, blood vessels, and extracellular matrix

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