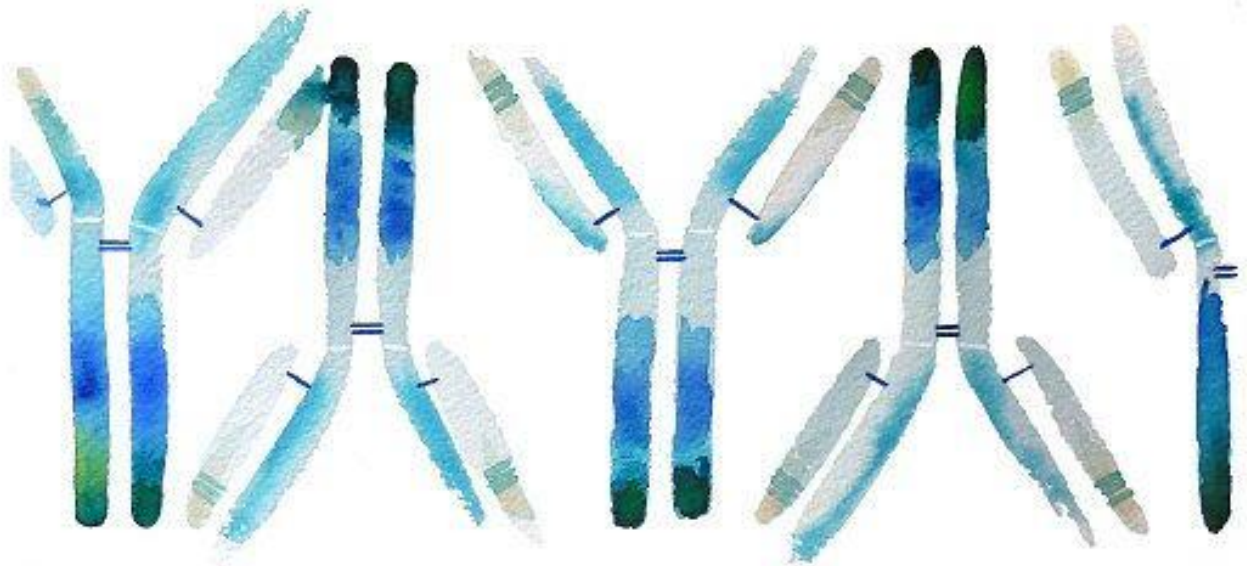
Medical Immunology



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Cancer immunology

Antibodies and antigens

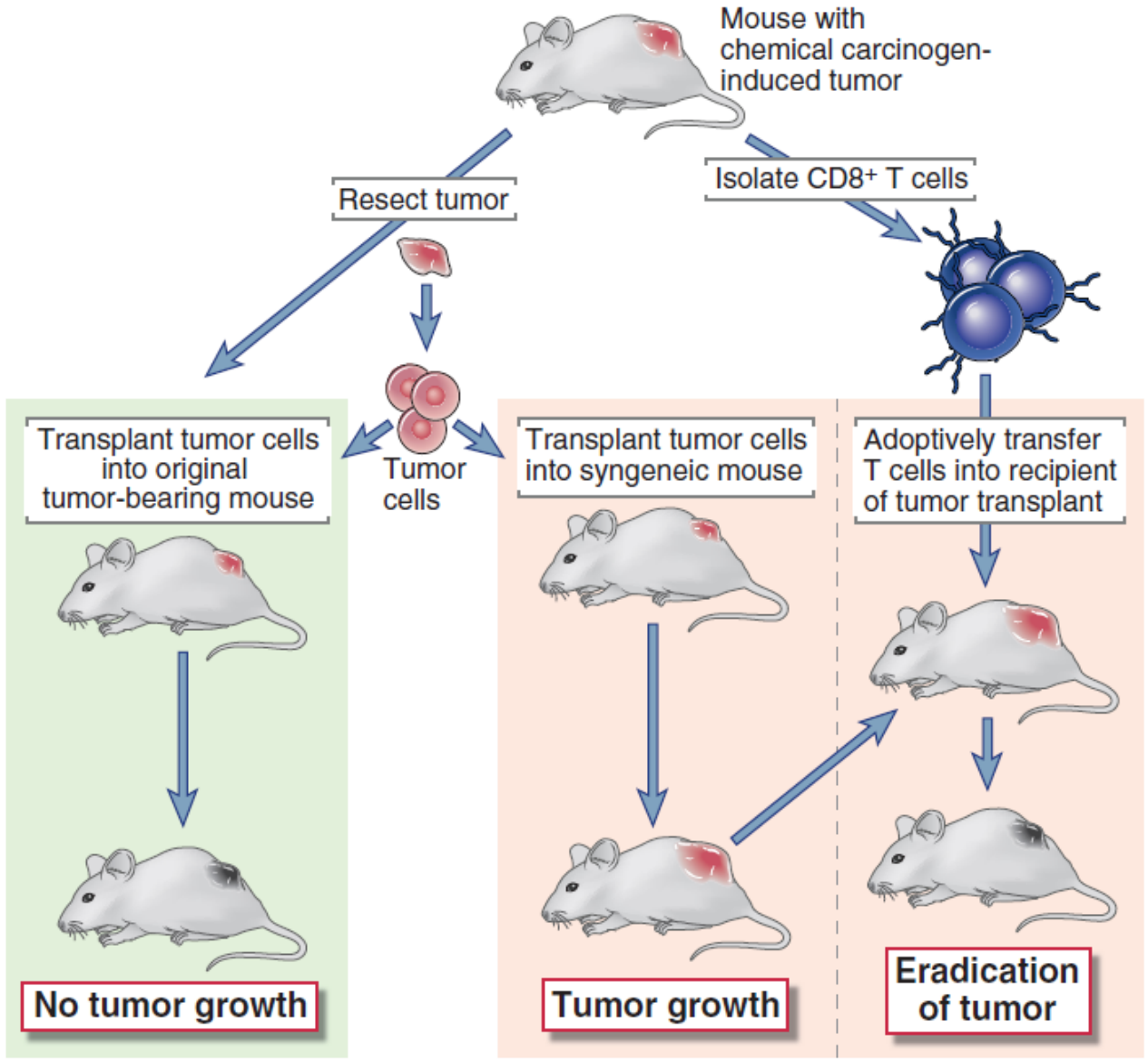
In this lecture we will discuss:

- Cancer immunology.
- CAR T cells.

Immunity to cancers - overview

- The existence of immune surveillance has been demonstrated by the increased incidence of some types of tumors in immunocompromised experimental animals and humans.

- Although the overall importance of immune surveillance has been controversial, it is now clear that the innate and adaptive immune systems do react against many tumors, and exploiting these reactions to specifically destroy tumors remains an important goal of tumor immunologists.



Immunity to cancers - overview

- **Tumors stimulate specific, adaptive immune responses.**

Clinical observations and animal experiments have established that although tumor cells are derived from host cells, the tumors elicit immune responses.

Histopathologic studies show that many tumors are surrounded by mononuclear cell infiltrates composed of **T lymphocytes, natural killer (NK) cells, and macrophages**, and that activated lymphocytes and macrophages are present in **lymph nodes draining the sites of tumor growth**

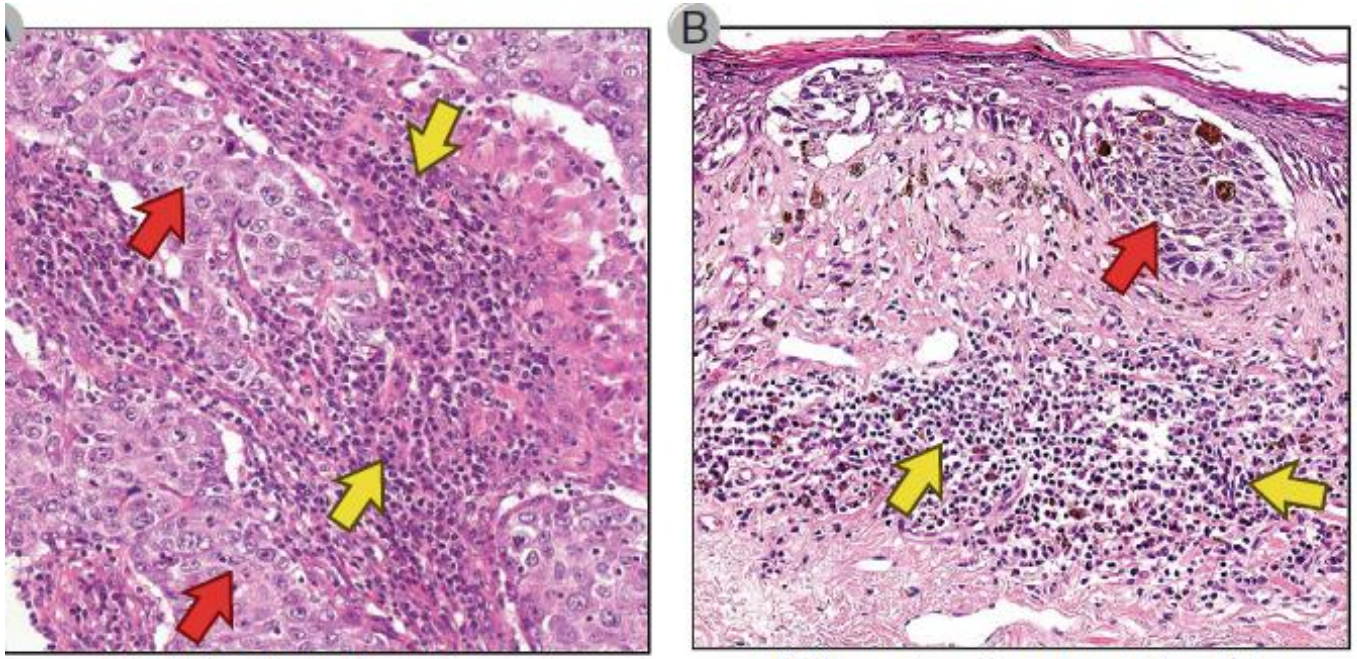


FIGURE 17–1 Lymphocytic inflammation associated with certain tumors. A, Medullary breast carcinoma. **B,** Malignant melanoma. Red arrows indicate malignant cells. Yellow arrows indicate lymphocyte-rich inflammatory infiltrates.

- **Immune responses frequently fail to prevent the growth of tumors**

The similarities of antigens with normal tissue, the immunosuppressive environment of many cancers and the rapid growth and spread of tumors may overwhelm the capacity of the immune system to effectively control a tumor.

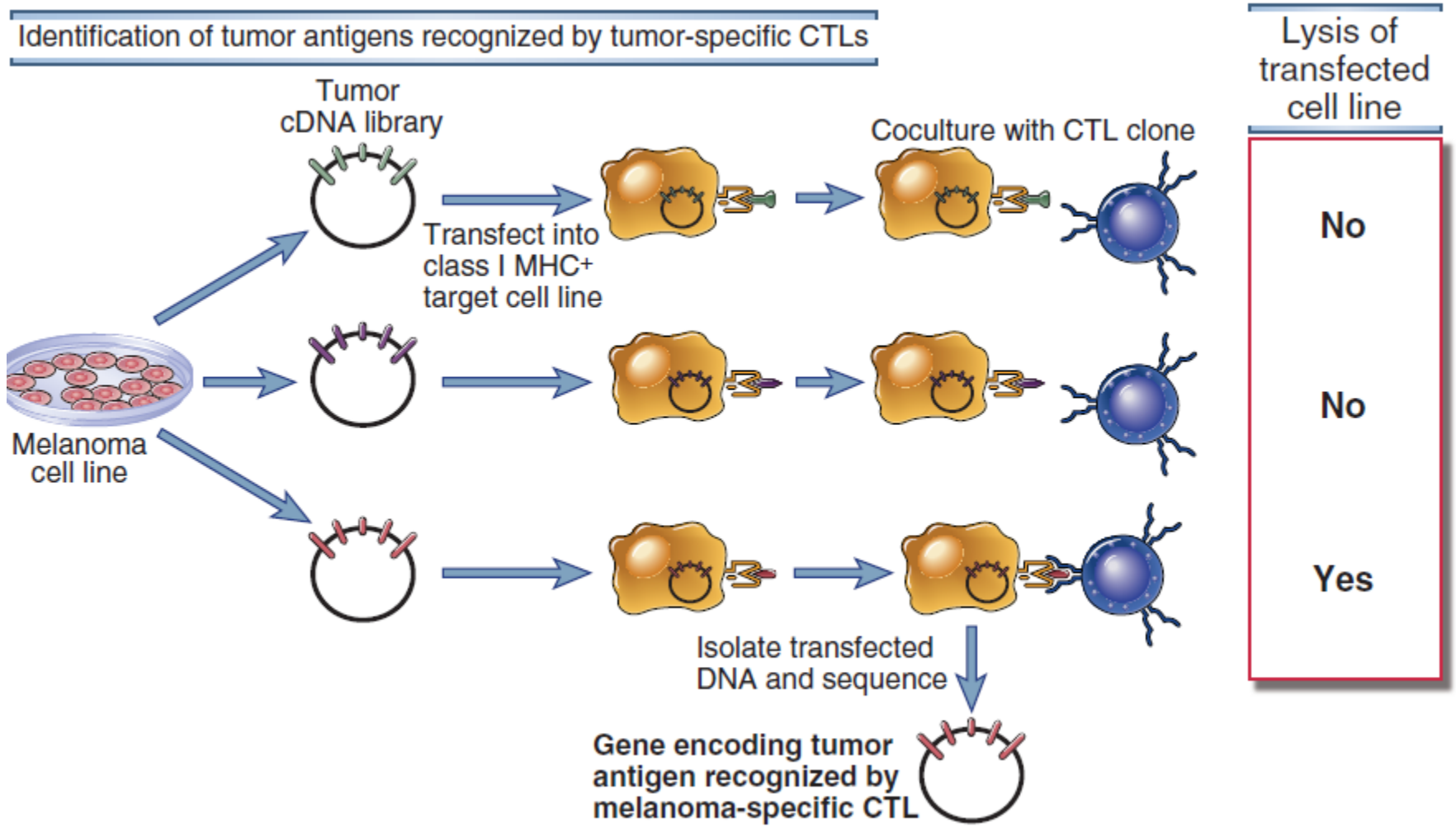
Various biochemical and molecular genetic approaches have been used to identify **tumor antigens**. For tumor antigens recognized by CD8+ cytotoxic T lymphocytes (CTLs), investigators have established cloned lines of tumor-reactive CTLs from cancer patients and used these as probes to specifically identify the relevant peptide antigens or the genes encoding the peptides.

Oncogenes and mutated tumor suppressor genes produce proteins that differ from normal cellular proteins and are, therefore, recognized **as tumor antigens**

Immunity to cancers – tumor antigens

TABLE 17–1 Tumor Antigens

Type of Antigen
Products of mutated oncogenes, tumor suppressor genes
Unmutated but overexpressed products of oncogenes
Mutated forms of cellular genes not involved in tumorigenesis
Products of genes that are silent in most normal tissues
Normal proteins overexpressed in tumor cells
Products of oncogenic viruses
Oncofetal antigens
Glycolipids and glycoproteins
Differentiation antigens normally present in tissue of origin



Immunity to cancers – Innate effector mechanisms against tumors

- **NK cells** kill many types of tumor cells, especially cells that have **reduced class I MHC expression** and **express ligands for NK cell activating receptors**.

- In addition, NK cells can be targeted to **IgG antibody– coated tumor cells** by Fc receptors (FcγRIII or CD16).

- **Macrophages** are capable of both inhibiting and promoting the growth and spread of cancers, depending on their activation state.

- **Classically activated M1 macrophages, display various anti-tumor functions**. Through secretion of inflammatory cytokines like tumor necrosis factor (TNF), release of lysosomal enzymes, and reactive oxygen species.

- In contrast, **M2 macrophages may contribute to tumor progression**. These cells secrete vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and other soluble factors that promote tumor angiogenesis

- The principal mechanism of adaptive tumor immunity is killing of tumor cells by **CD8+ CTLs**.

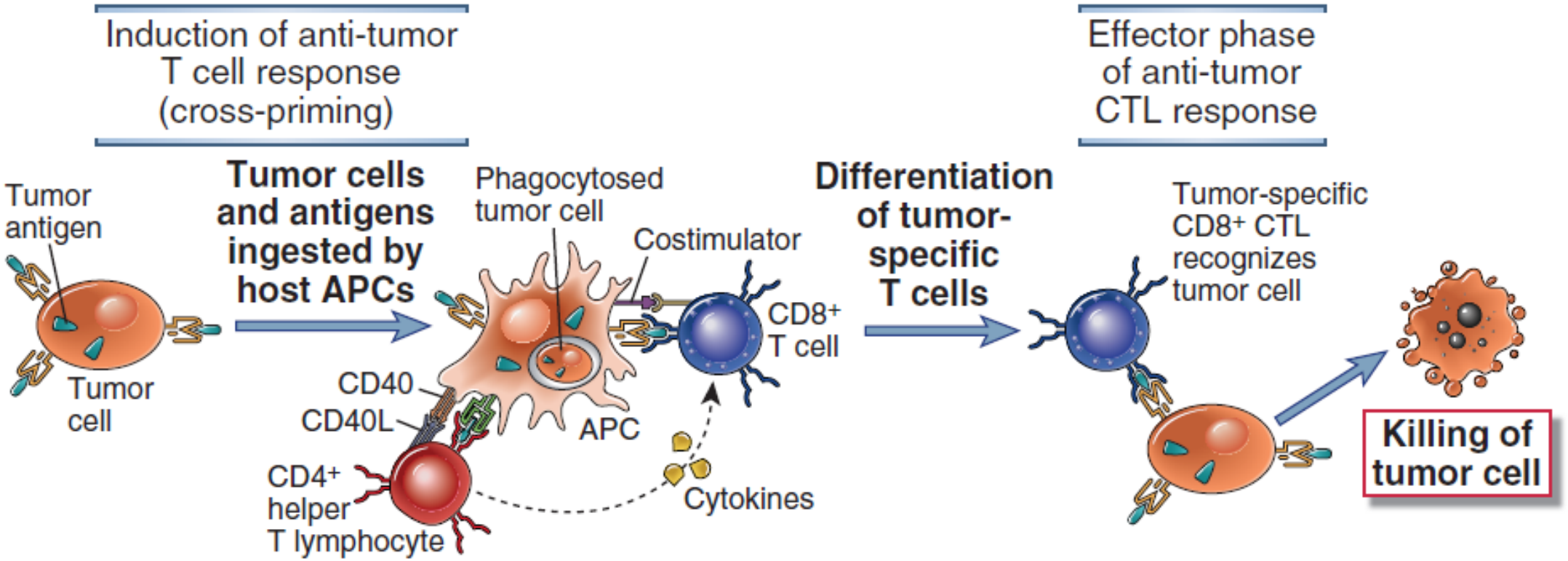
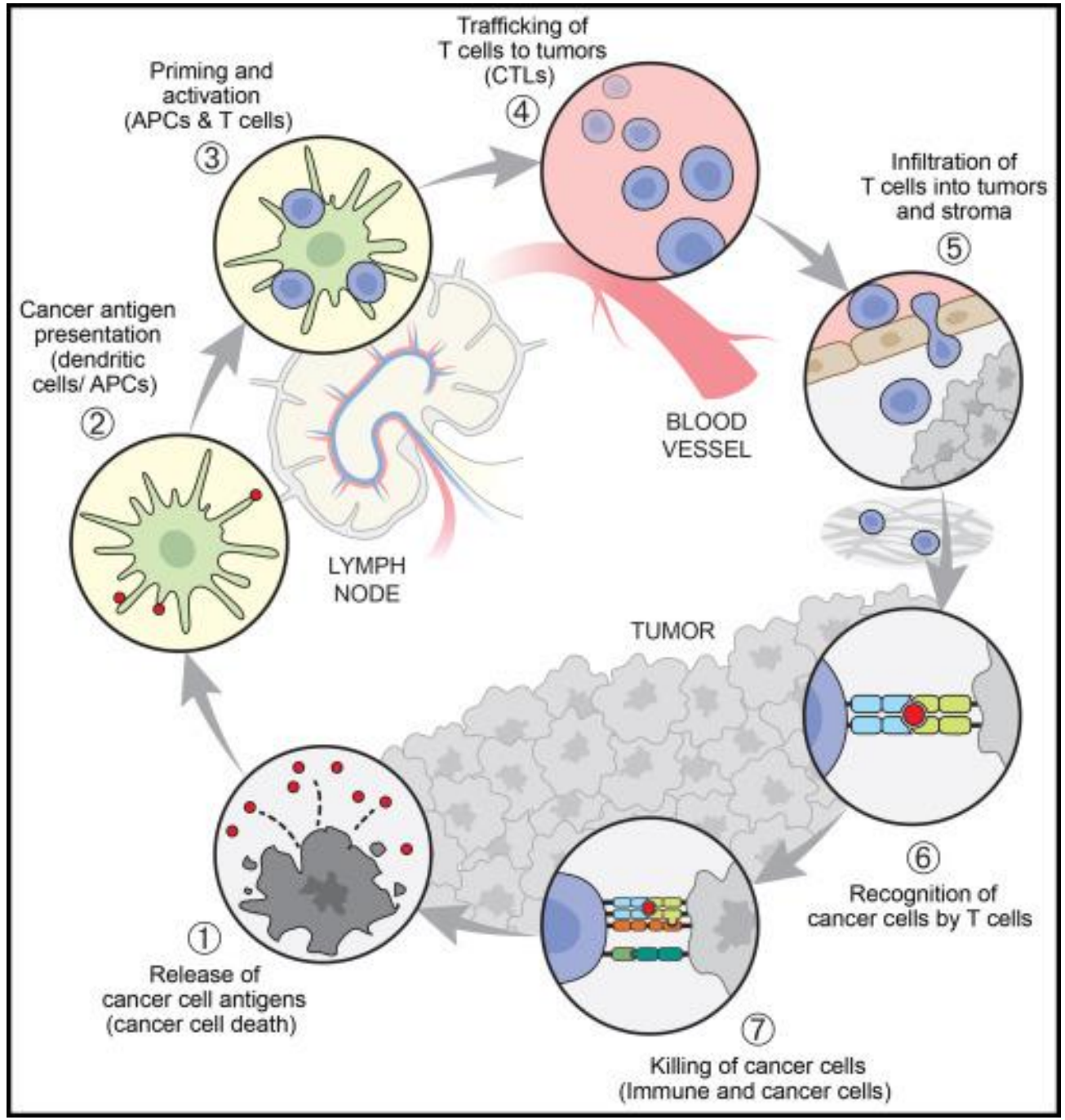


FIGURE 17–4 Induction of T cell responses to tumors. $CD8^+$ T cell responses to tumors may be induced by cross-priming (cross-presentation), in which the tumor cells or tumor antigens are taken up, processed, and presented to T cells by professional antigen-presenting cells (APCs). In some cases, B7 costimulators expressed by the APCs provide the second signals for differentiation of $CD8^+$ T cells. The APCs may also stimulate $CD4^+$ helper T cells, which provide the second signals for CTL development. Differentiated CTLs kill tumor cells without a requirement for costimulation or T cell help. (The roles of cross-presentation and $CD4^+$ helper T cells in CTL responses are discussed in Chapters 6 and 9.)

- **CD4+** cells may play a role in anti-tumor immune responses by providing cytokines for effective CTL development. Helper T cells specific for tumor antigens may secrete cytokines, such as TNF and IFN-γ, that can increase tumor cell class I MHC expression and sensitivity to lysis by CTLs. IFN-γ may also activate macrophages to kill tumor cells.

- **Antibodies** may kill tumor cells by **activating complement or by antibody-dependent cell mediated cytotoxicity**, in which Fc receptor–bearing macrophages or NK cells mediate the killing. However, the ability of antibodies to eliminate tumor cells has been demonstrated largely in vitro, and there is little evidence for effective humoral immune responses against tumors.

The cancer-immunity cycle

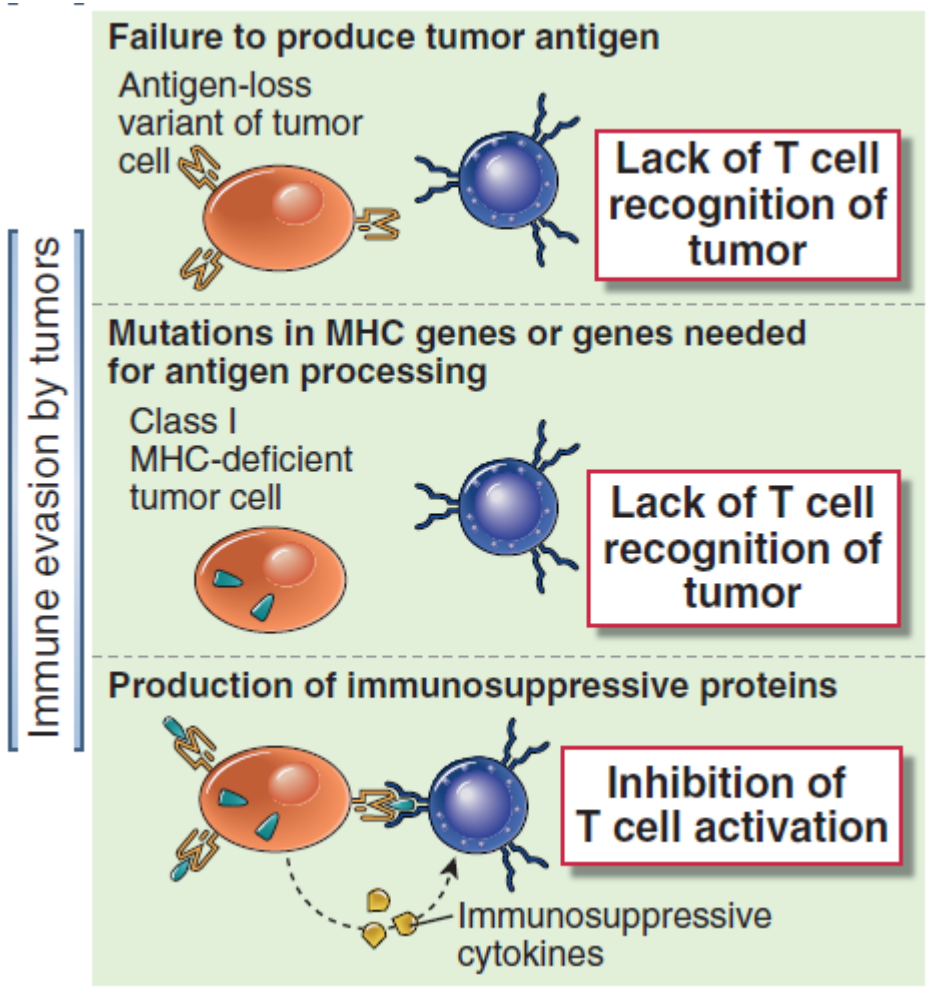


Immunity to cancers – Immune Evasion by Tumor Cells

- T cell responses to some tumors are inhibited by the involvement of **CTLA-4 or PD-1**, two of the best defined inhibitory pathways in T cells

- Tumors may fail to induce strong effector T cell responses because most tumor cells **do not express costimulators or class II MHC molecules**

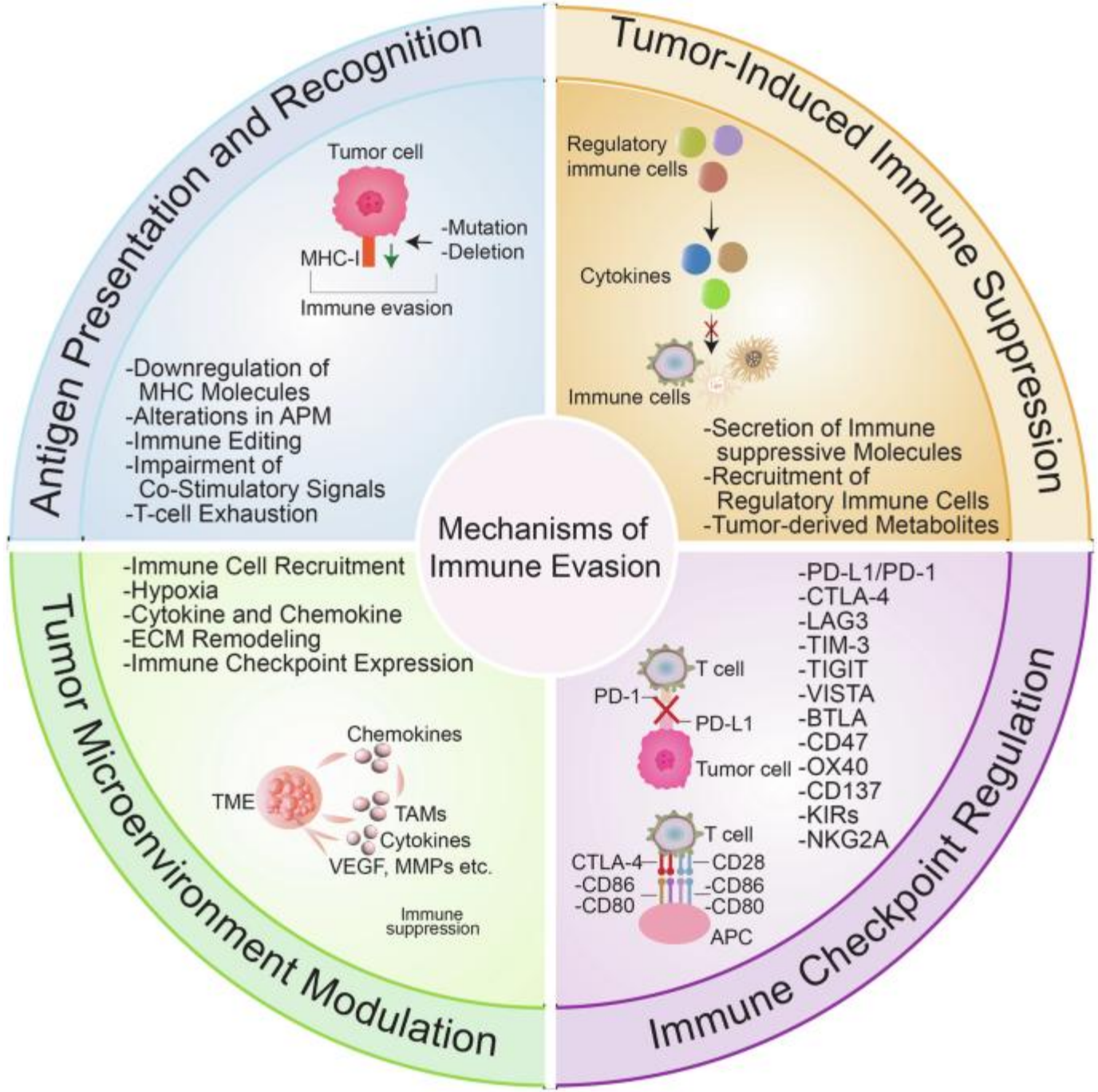
- Secreted products of tumor cells may suppress anti-tumor immune responses. An example of an immunosuppressive tumor product is TGF-β



- **Tumor-associated macrophages, usually M2,** may promote tumor growth and invasiveness by altering the tissue microenvironment and by suppressing T cell responses.

- **Regulatory T cells** may suppress T cell responses to tumors. The numbers of regulatory T cells are increased in tumor-bearing individuals.

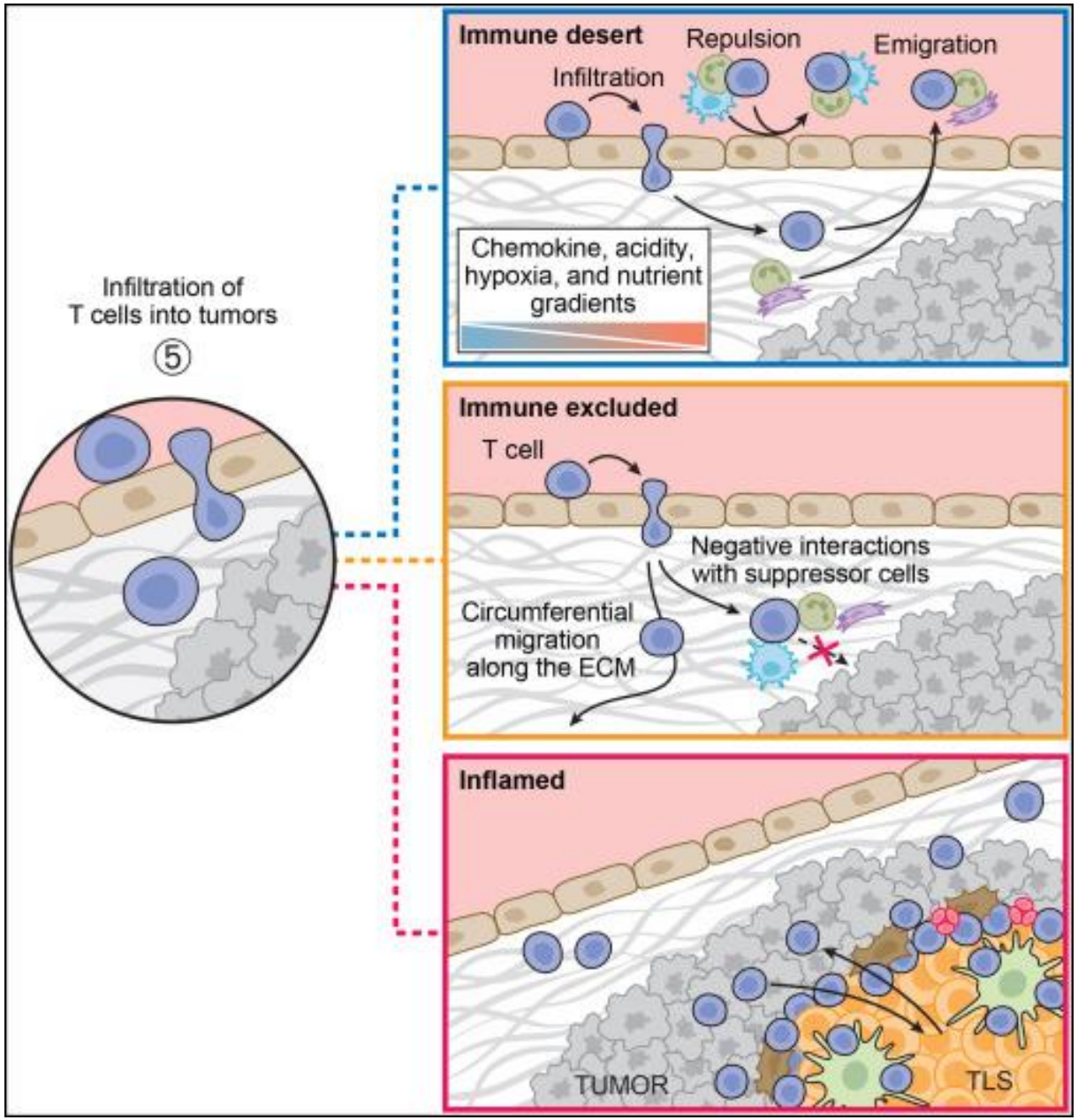
- **Myeloid-derived suppressor cells (MDSCs)** are immature myeloid precursors that are recruited from the bone marrow and accumulate in tumors and suppress anti-tumor innate and T cell responses.


Antigen Presentation and Recognition
Tumor cell
MHC-I
-Mutation
-Deletion
Immune evasion
-Downregulation of MHC Molecules
-Alterations in APM
-Immune Editing
-Impairment of Co-Stimulatory Signals
-T-cell Exhaustion
Tumor-Induced Immune Suppression
Regulatory immune cells
Cytokines
Immune cells
-Secretion of Immune suppressive Molecules
-Recruitment of Regulatory Immune Cells
-Tumor-derived Metabolites
Mechanisms of Immune Evasion
Tumor Microenvironment Modulation
-Immune Cell Recruitment
-Hypoxia
-Cytokine and Chemokine
-ECM Remodeling
-Immune Checkpoint Expression
Chemokines
TME
TAMs
Cytokines
VEGF, MMPs etc.
Immune suppression
Immune Checkpoint Regulation
T cell
PD-1
PD-L1
Tumor cell
-PD-L1/PD-1
-CTLA-4
-LAG3
-TIM-3
-TIGIT
-VISTA
-BTLA
-CD47
-OX40
-CD137
-KIRs
-NKG2A
T cell
CTLA-4
-CD86
-CD80
CD28
-CD86
-CD80
APC

Tumor immunotypes

- Tumors can be viewed as assuming different immunological phenotypes, or “immunotypes”.

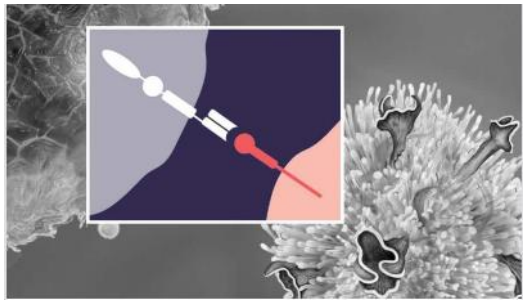
- The three classical immunotypes, immune inflamed, immune excluded, and immune desert, are defined, respectively, as tumors containing abundant immune infiltrate, tumors where T cell infiltrate is limited to tumor stroma as opposed to the tumor parenchyma, and tumors that do not exhibit immune infiltrate



What is immunotherapy?

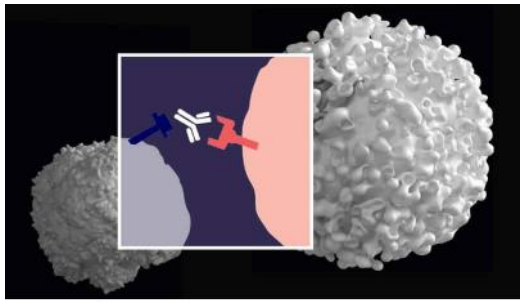
- Cancer immunotherapy, also known as immuno-oncology, is a form of cancer treatment that uses the power of the body's own immune system to prevent, control, and eliminate cancer.

Cancer immunotherapy forms



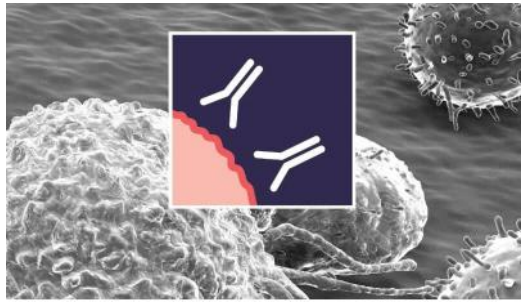
cellular immunotherapy

Cancer Vaccines



Immunomodulators – Checkpoint Inhibitors

Oncolytic Virus Therapy



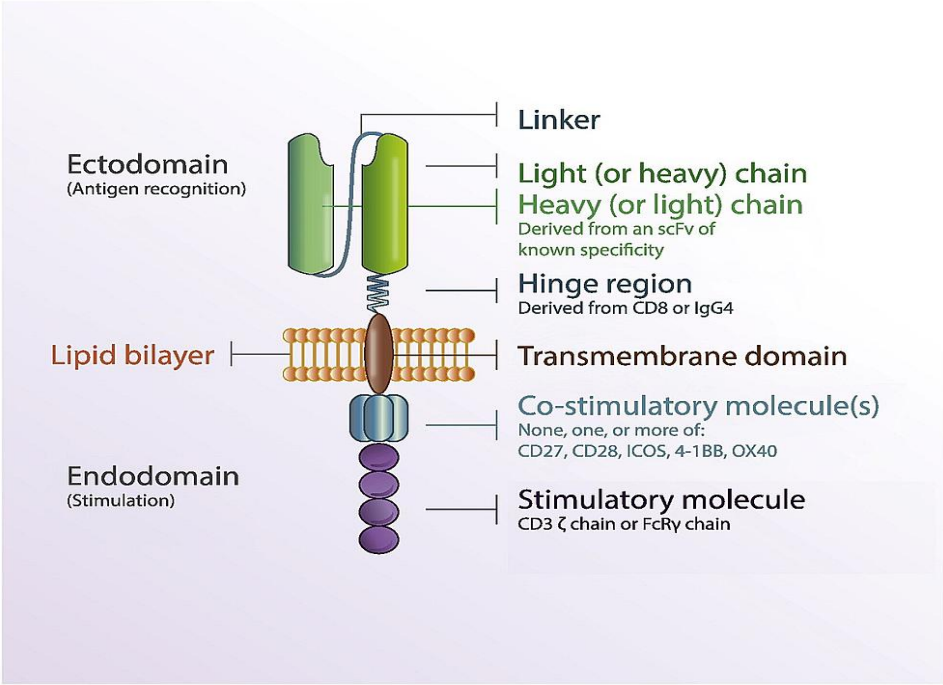
Targeted Antibodies

Cellular immunotherapy - chimeric Antigen Receptor T cell (CAR T cells)

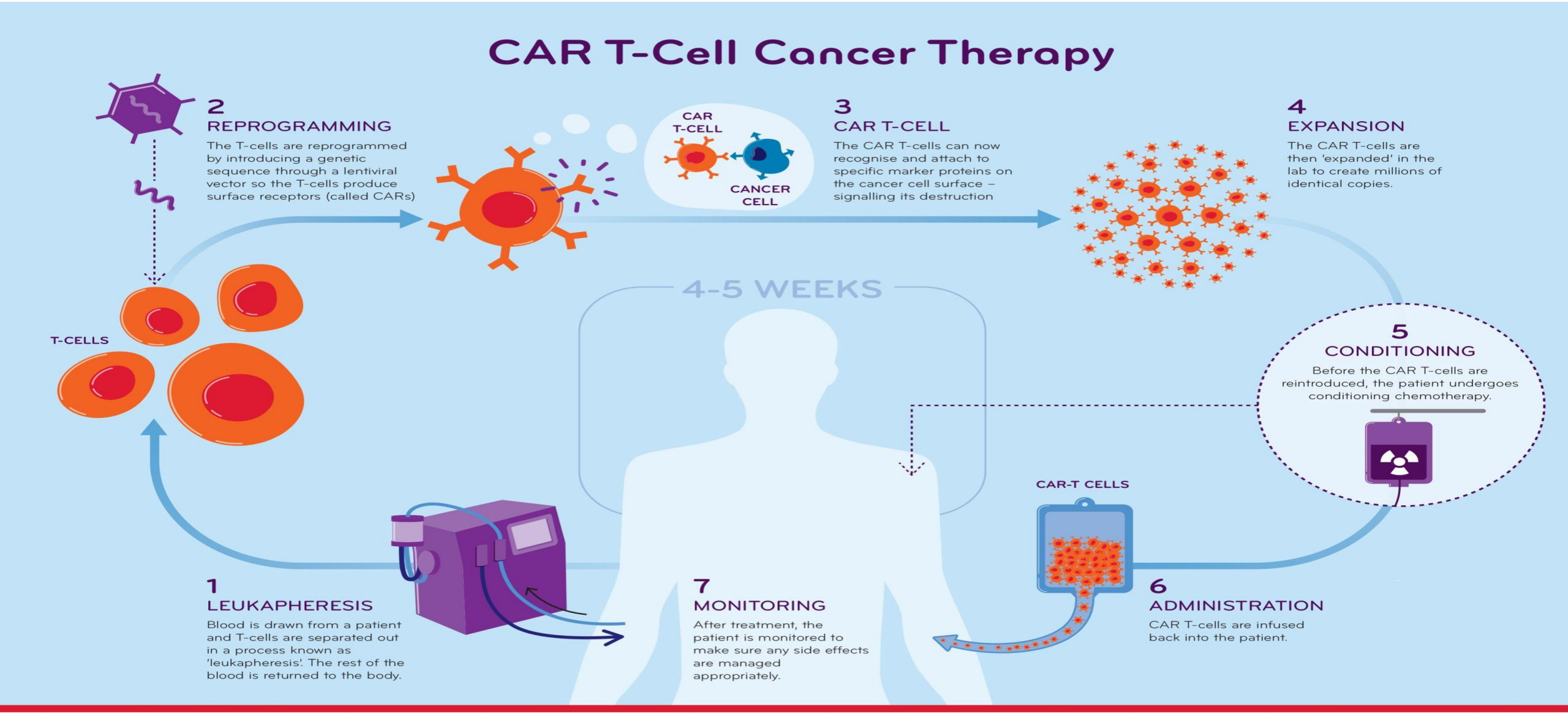
- CARs are engineered synthetic receptors that function to redirect lymphocytes, most commonly T cells, **to recognize and eliminate cells expressing a specific target antigen**.

- CAR binding to target antigens expressed on the cell surface is independent from the MHC receptor resulting in T cell activation and powerful anti-tumor responses.

- CARs are modular synthetic receptors that consist of four main components:
- an extracellular target antigen-binding domain
- a hinge region
- a transmembrane domain
- one or more intracellular signaling domains



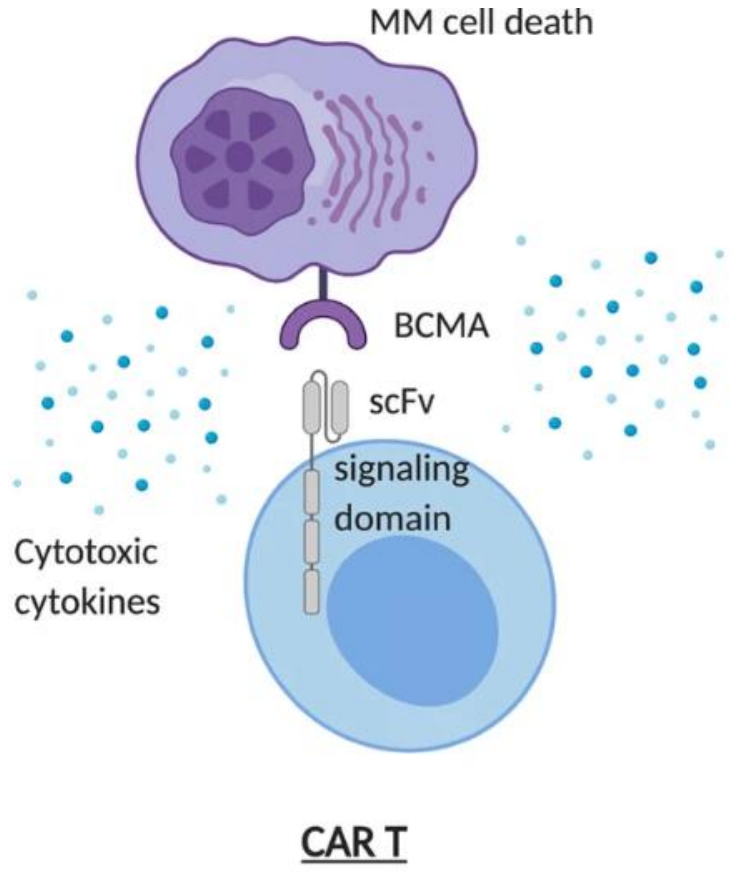
Tumor immunotypes



Cellular immunotherapy - chimeric Antigen Receptor T cell (CAR T cells)

- **Chimeric antigen receptor T (CAR-T)** cell therapies have transformed the treatment of **B-cell malignancies** and multiple myeloma by redirecting activated T cells to CD19- or BCMA-expressing tumor cells.

- CAR T-cell therapy challenges include severe side effects (like cytokine release syndrome and neurotoxicity), **limited success in solid tumors** due to **antigen escape** and **immunosuppressive environments**, **poor cell trafficking**, T-cell exhaustion, **high costs**, logistical complexities (long manufacturing), and **potential off-target toxicities**, making access difficult and requiring advanced engineering to overcome these hurdles.



Chimeric antigen receptor (CAR)-T cells. The ectodomain of the BCMA scFv on the CAR-T cells binds to BCMA on the surface of MM cells. This leads to activation of the CAR-T cells which release cytotoxic cytokines and cause MM cell death

- It remains the case that far fewer than half of patients have durable outcomes with immunotherapy, even in combination. Understanding features to predict response or understanding mechanisms of resistance continues to be a major focus of investigation both pre-clinically and in the clinic.

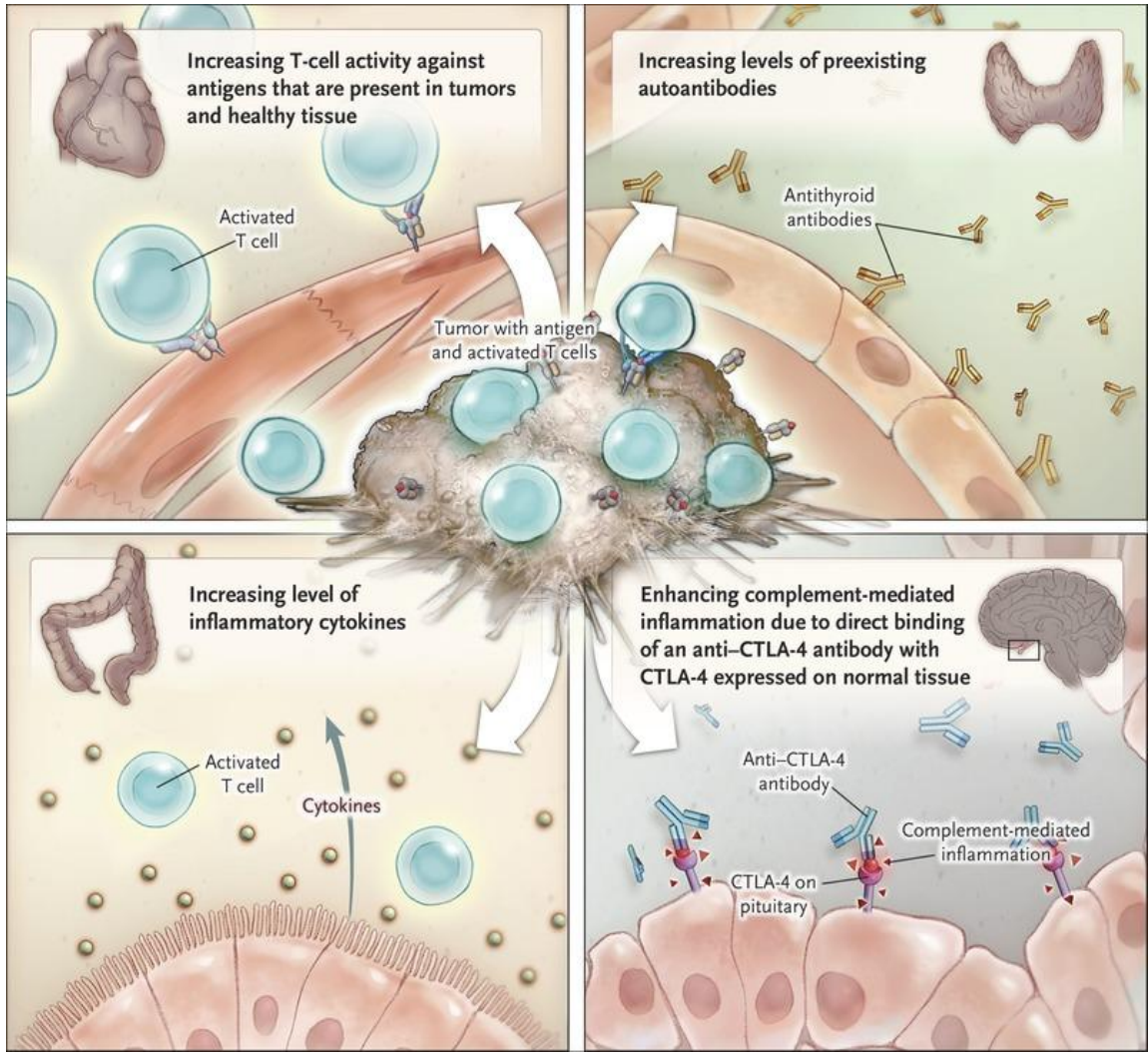
- These factors may be intrinsic to the tumor, the TME, or a reflection of patient genetics, microbiome, metabolism, or pharmacologic status but in each case must reflect the site of a rate limiting step in the CI cycle

MECHANISMS OF IRAES

- Immune-related adverse events (irAEs) can occur as a result of immune checkpoint inhibitor (ICI) therapy, which activates the immune system to target cancer cells.Such as:

1. Tissue-specific autoimmune reactions
2. Increasing levels of autoantibodies
3. Increasing levels of inflammatory cytokines
4. Enhance complement mediated activation

- CTLA-4 related adverse events are different from those developed with anti-PD1 therapy since CTLA-4 inhibits T cells in the beginning of the immune response while PD-1 blocks T-cell in peripheral tissues and in a more advanced step of the immune response



irAEs efficacy

- In retrospective studies, the presence of irAEs has been **associated with clinical benefit.**
- ICIs can induce side effects through the inflammation with lymphocyte infiltration at any organ and consequently a system dysfunction.
- **Most irAEs are mild and transient**, nevertheless, sometimes they can be life-threatening. In fact, this can limit retreatment with ICIs after a toxicity or also it can lead to permanent dysfunctions and in some cases, patients may not recover from the adverse event.
- Despite this, recent publications have reported a relationship between irAEs and clinical efficacy in cancer patients in terms of response rate, PFS and OS.

Immunotherapy biomarkers

- There is a subset of patients who benefit most from immunotherapy with long-term survival. **The identification of these patients through biomarkers or specific features has been a crucial point for the scientific community in recent past year.**
- In the context of cancer immunotherapy, biomarkers can provide insights into each patient's individual cancer—its genetic makeup, its behavior, and its interactions with the immune system—which doctors can then use to determine the approach most likely to benefit a **particular person.**

What types of biomarkers are there?

Pre-treatment Biomarkers

•Diagnostic: What type of cancer is it?
•Prognostic: What is the expected outlook?
•Predictive: How likely is it that this treatment will work? Are side effects likely to occur?

Biomarkers during and after treatment

•Short-Term Monitoring: Is the treatment working? Have any side effects arisen?
•Extended Monitoring: Is the cancer still stable or in remission?

Immunotherapy biomarkers

1.PD-1/PD-L1 Expression: High levels of PD-L1 in tumors are associated with a higher likelihood of response to PD-1/PD-L1 checkpoint immunotherapy, although patients without PD-L1 expression can still respond due to the dynamic nature of PD-L1 expression.

2.Pre-Existing Immune Responses: The presence of CD8+ "killer" T cells within tumors, as well as higher diversity of T cells and cell-killing gene signatures, is associated with improved outcomes and increased likelihood of benefiting from PD-1/PD-L1 checkpoint immunotherapies.

3.Tumor Mutations: Tumor mutational burden (TMB), which reflects the number of mutations in a tumor, is a biomarker that predicts better response to checkpoint immunotherapy. High TMB is also associated with pre-existing immune responses and PD-1/PD-L1 expression.

4.Individual Mutations: Specific mutations in tumors can lead to primary or acquired resistance to immunotherapy, but they can also serve as targets for personalized immunotherapies, such as vaccines tailored to a patient's cancer.

5.Tumor-Associated Proteins: Abnormal expression of proteins, such as HER2 or NY-ESO-1, on cancer cells can be targeted by immunotherapies, leading to improved outcomes in specific cancer types.

6.The Microbiome: The composition of bacteria in the gut microbiome can influence the effectiveness of PD-1/PD-L1 checkpoint immunotherapy, with more diverse gut bacteria and specific bacterial types being associated with better treatment response.

Cancer Immunotherapy

- Immunotherapy is established as a first-line standard of care for several cancers, either as a standalone treatment or in combination with other therapies like chemotherapy. Key factors for determining first-line use include cancer type, stage, and specific biomarkers.

Examples include:

- Melanoma: Immunotherapy, particularly checkpoint inhibitors (e.g., pembrolizumab, nivolumab), is the primary treatment for unresectable or metastatic melanoma, with the potential for long-term remission
- Non-Small Cell Lung Cancer (NSCLC): It is a cornerstone of first-line treatment for advanced NSCLC. Eligibility often depends on the expression level of the PD-L1 biomarker; patients with high expression may receive immunotherapy alone, while others might receive it in combination with chemotherapy.
- Colorectal Cancer: Immunotherapy is the first-line treatment for metastatic or unresectable colorectal cancer that is identified as Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR).

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 5. Antibodies and antigens