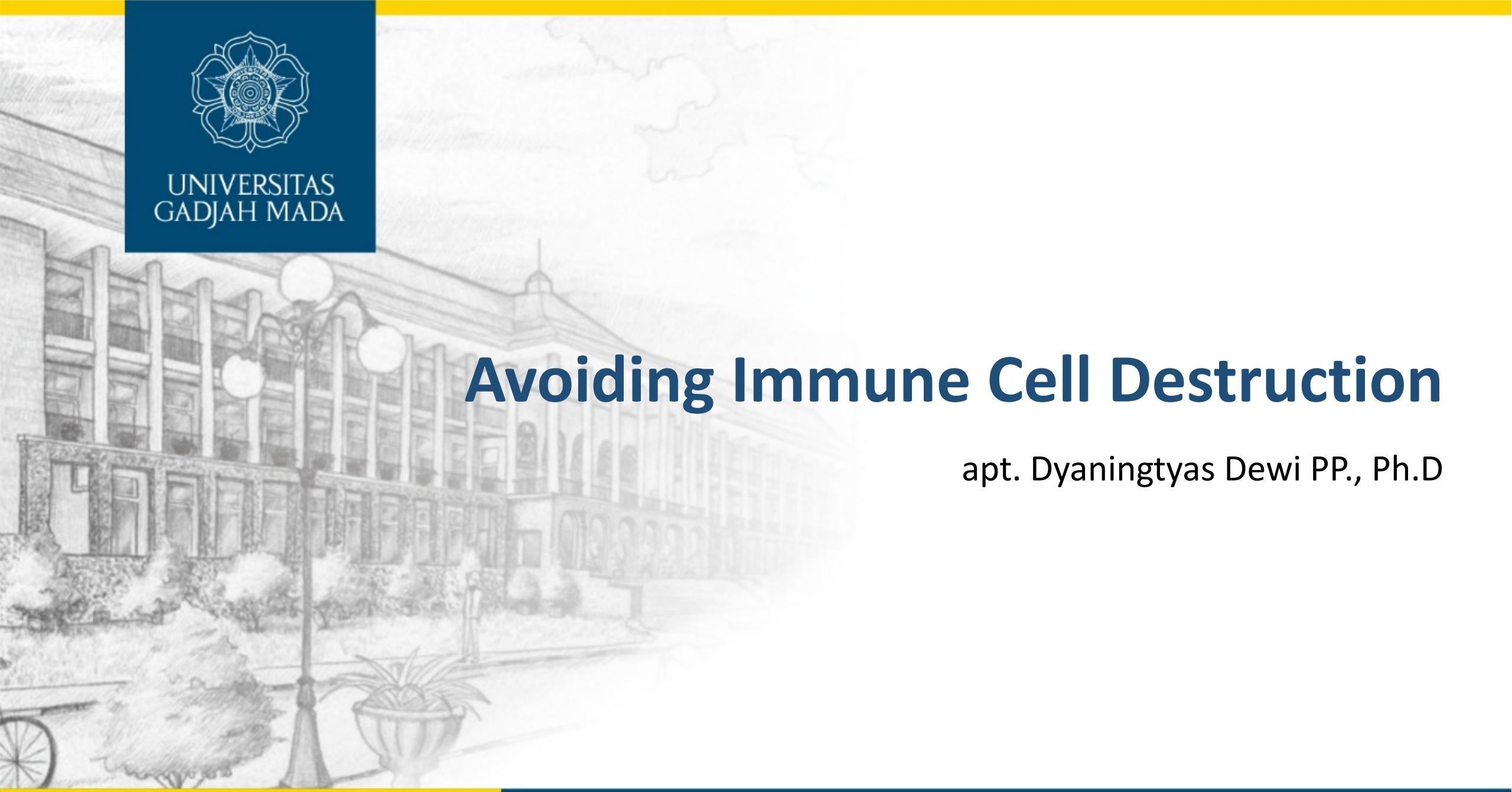

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Avoiding Immune Cell Destruction

apt. Dyaningtyas Dewi PP., Ph.D

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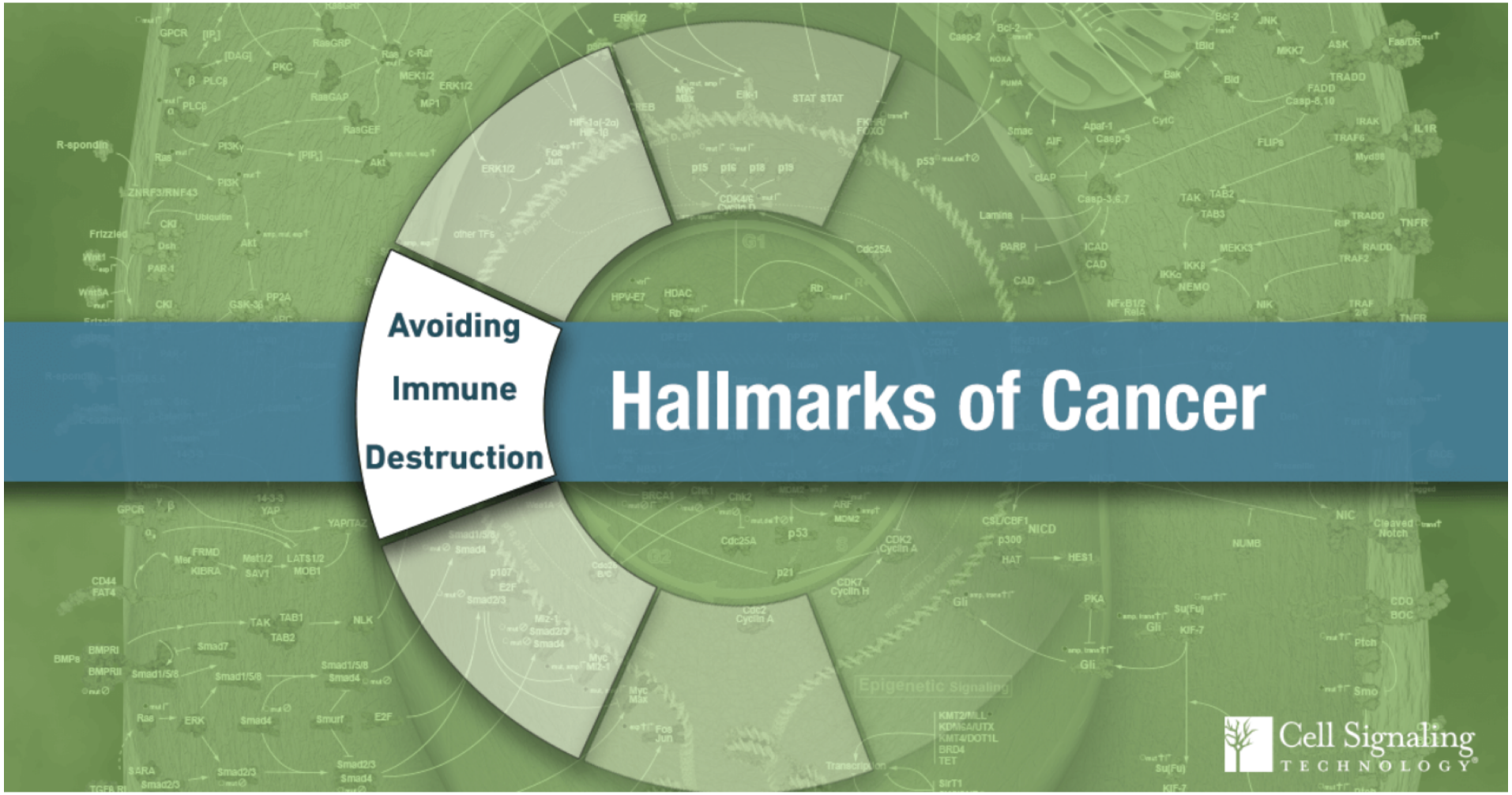
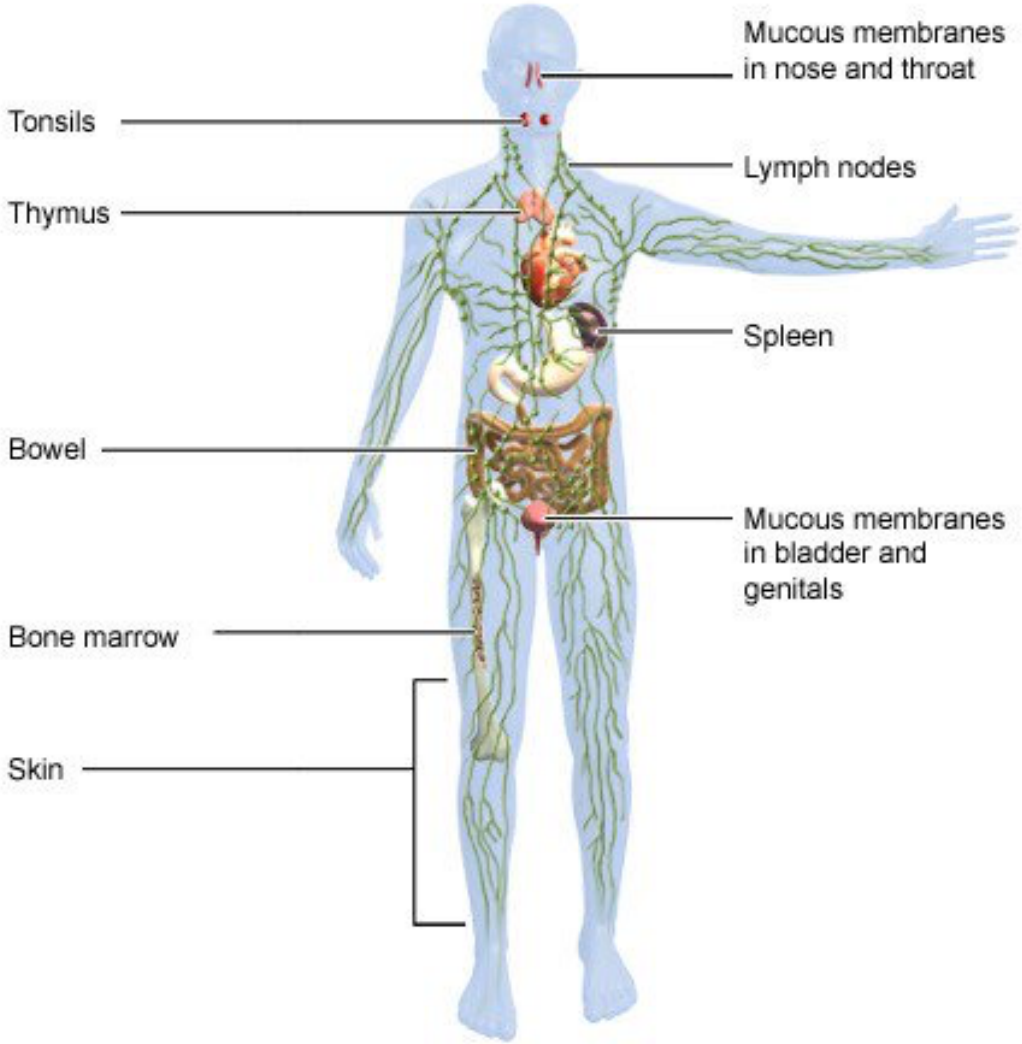
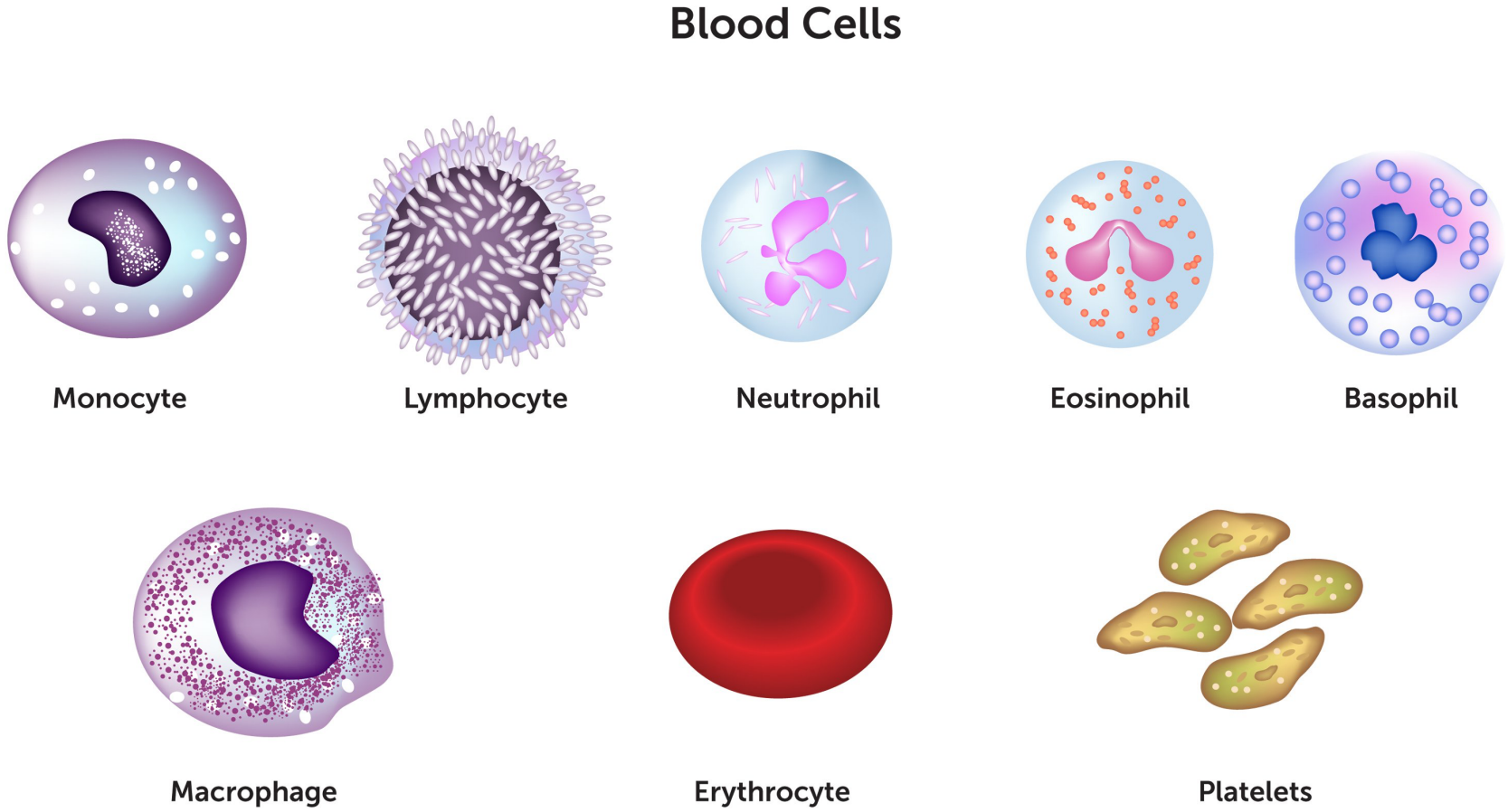


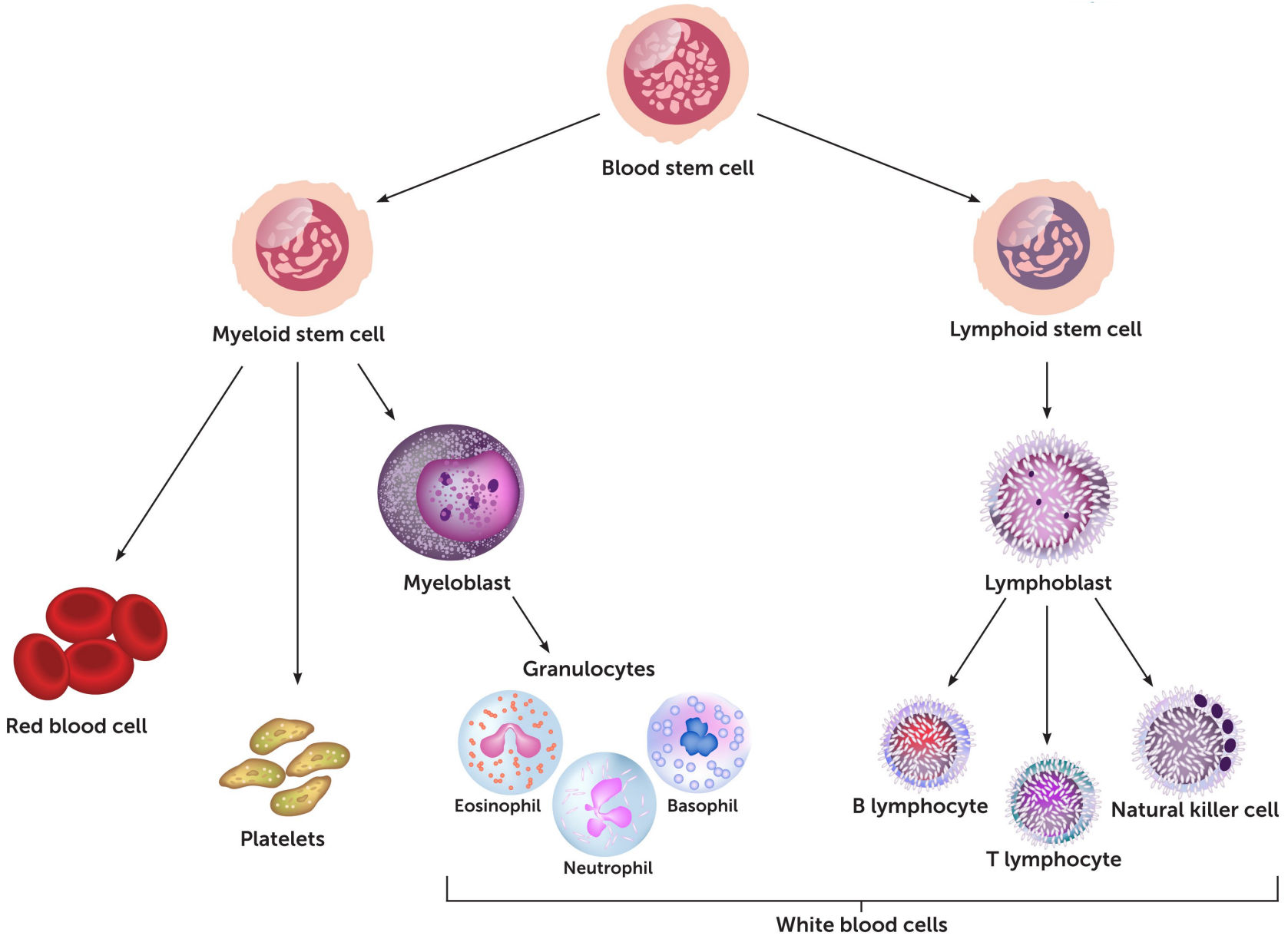
LOCALLY ROOTED, GLOBALLY RESPECTED

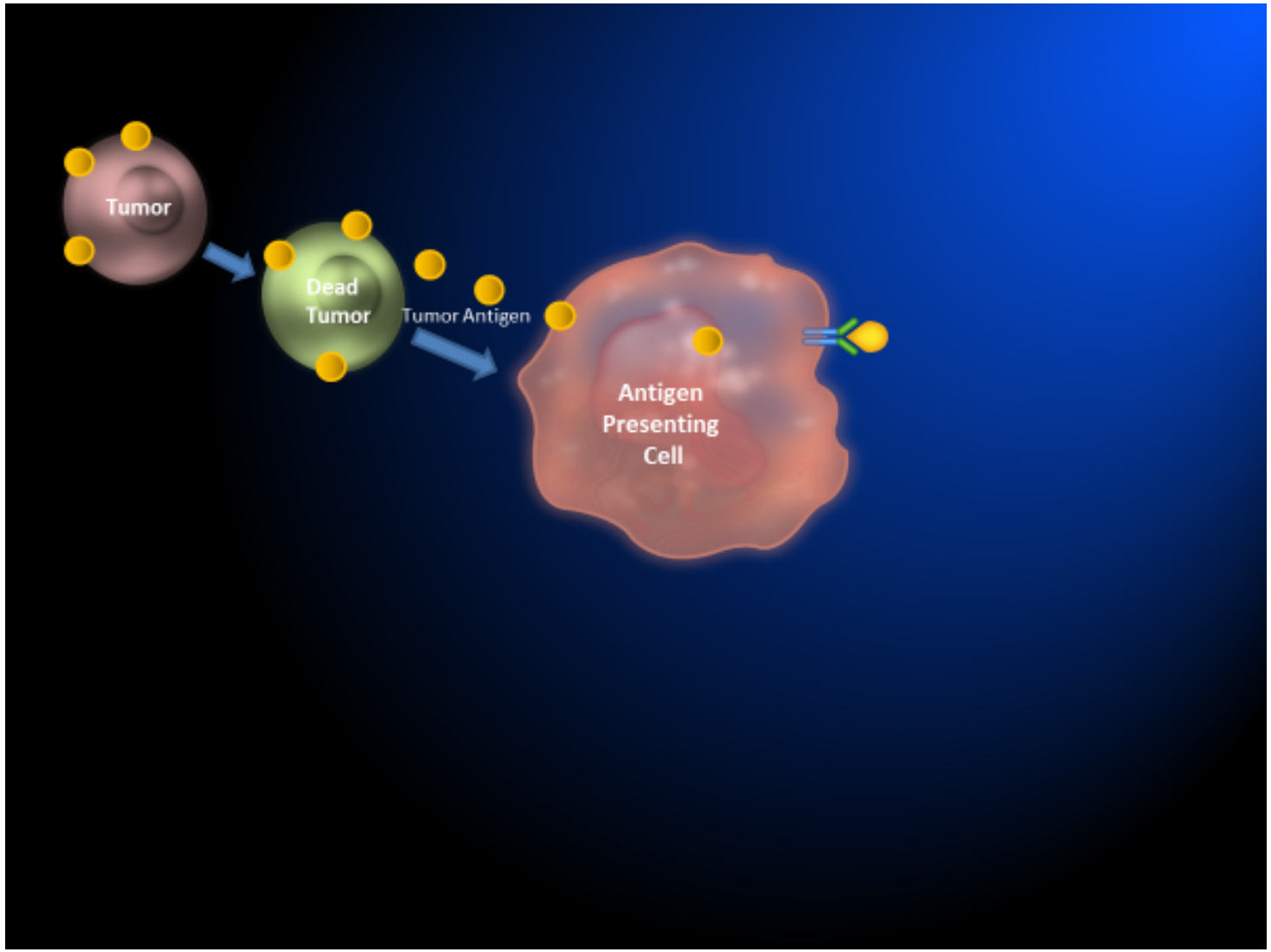


What are the parts of the immune system?

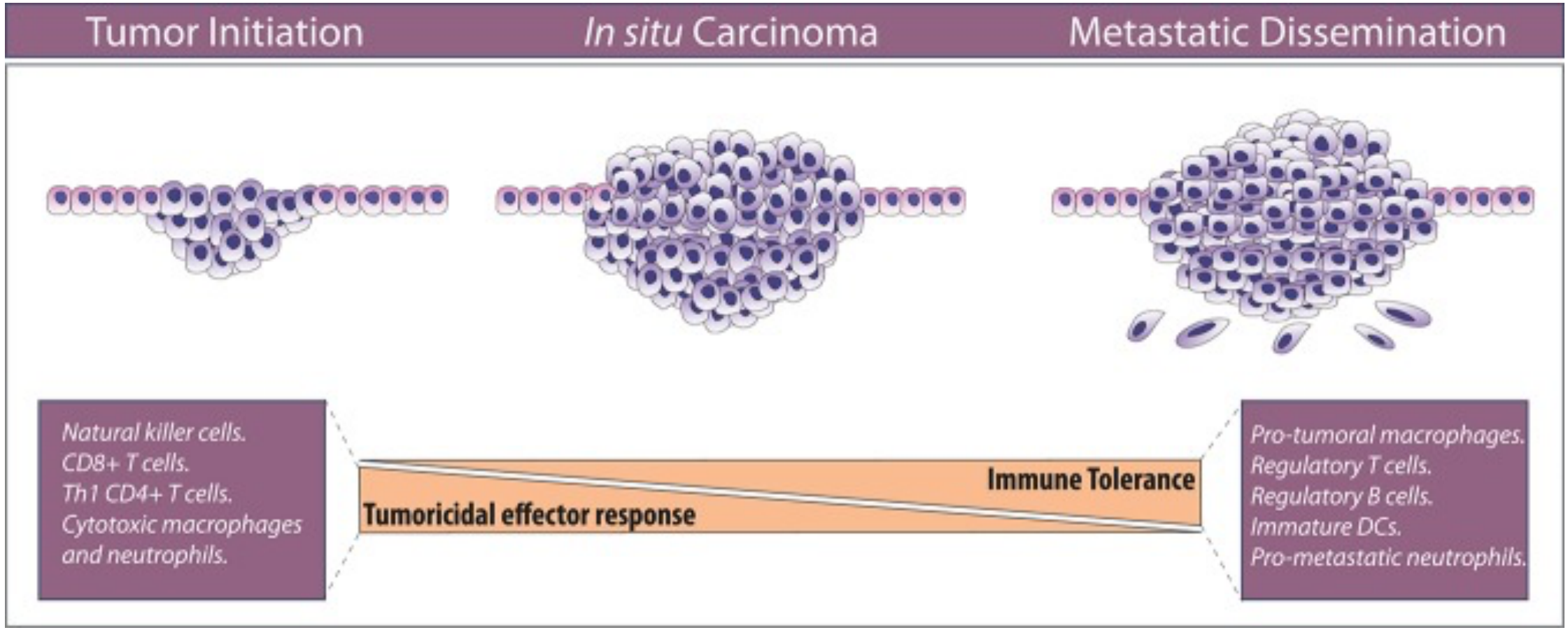
Kind of immune cells



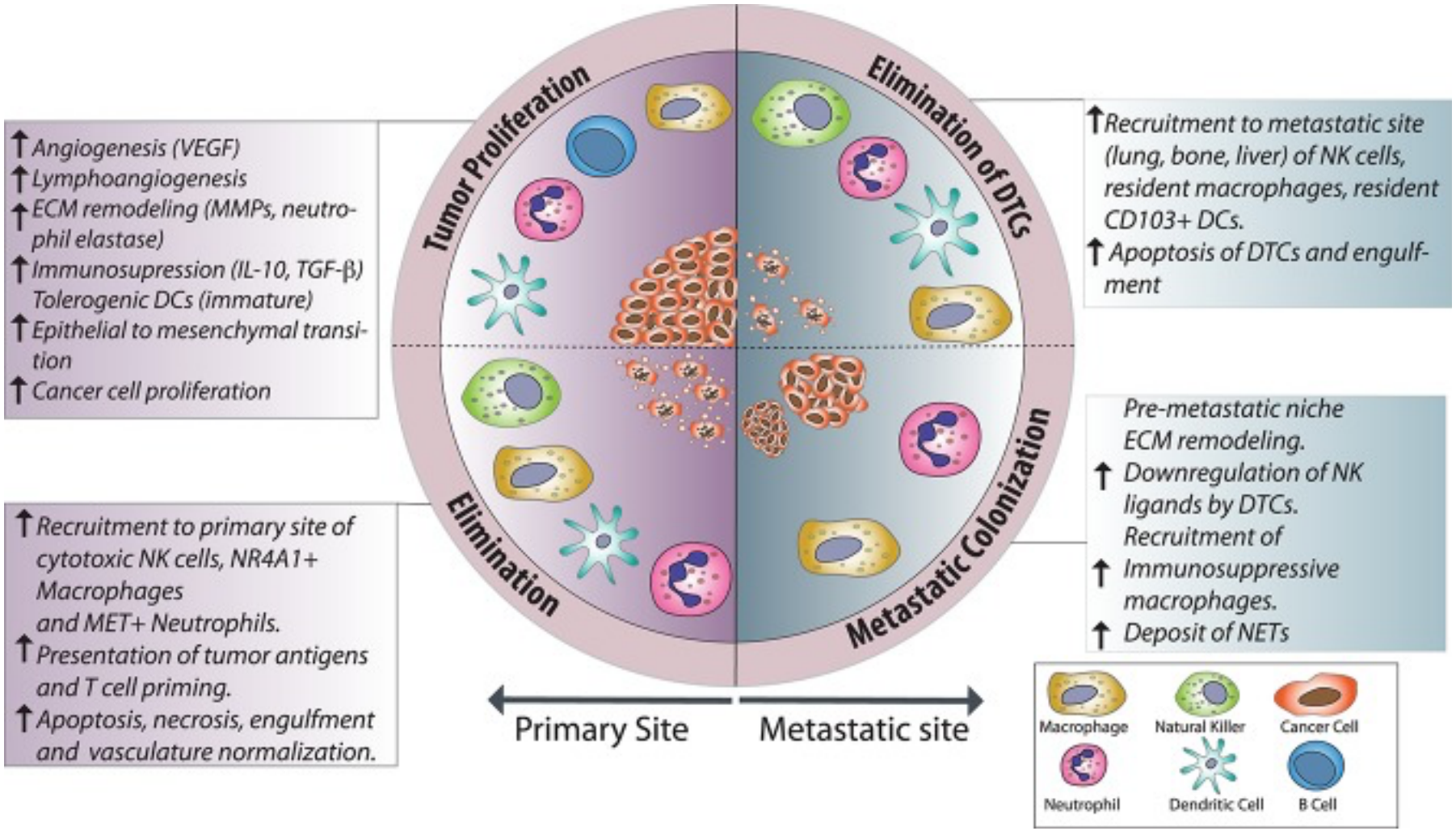

Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Red blood cell
Platelets
Myeloblast
Granulocytes
Eosinophil
Basophil
Neutrophil
Lymphoblast
B lymphocyte
T lymphocyte
Natural killer cell
White blood cells


Tumor
Dead Tumor
Tumor Antigen
Antigen Presenting Cell

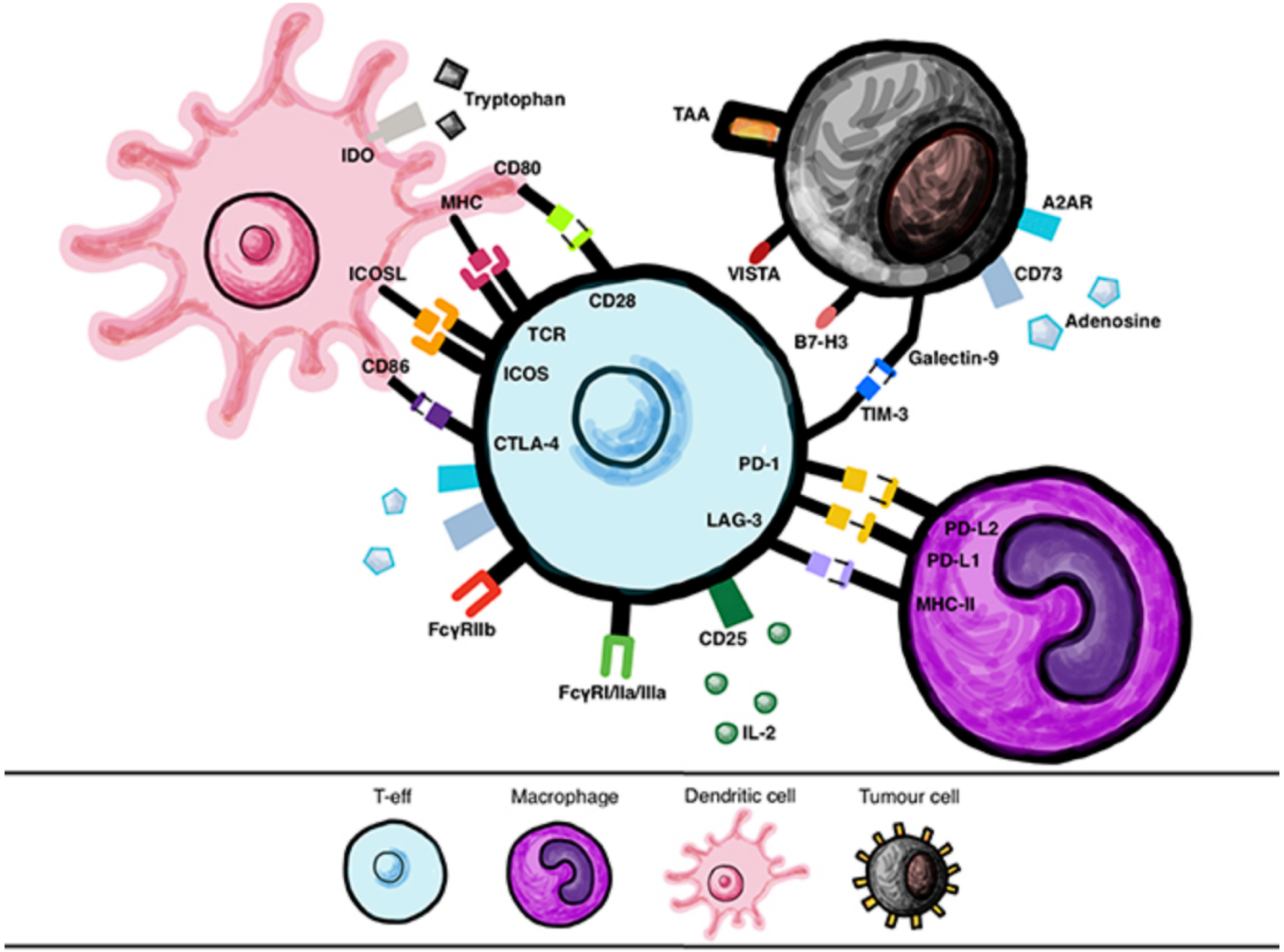
Cancer and immune cells



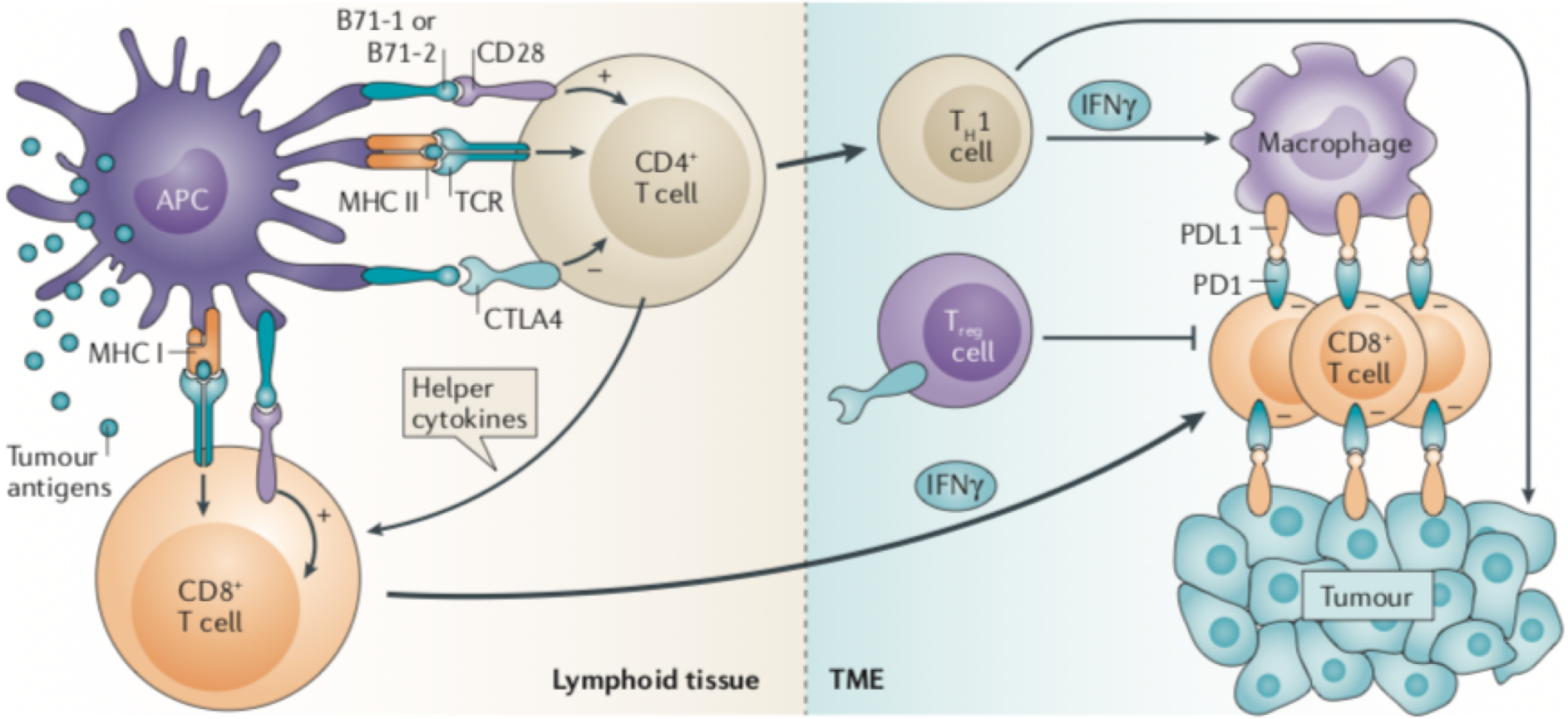
immune cells respond to cancer cells



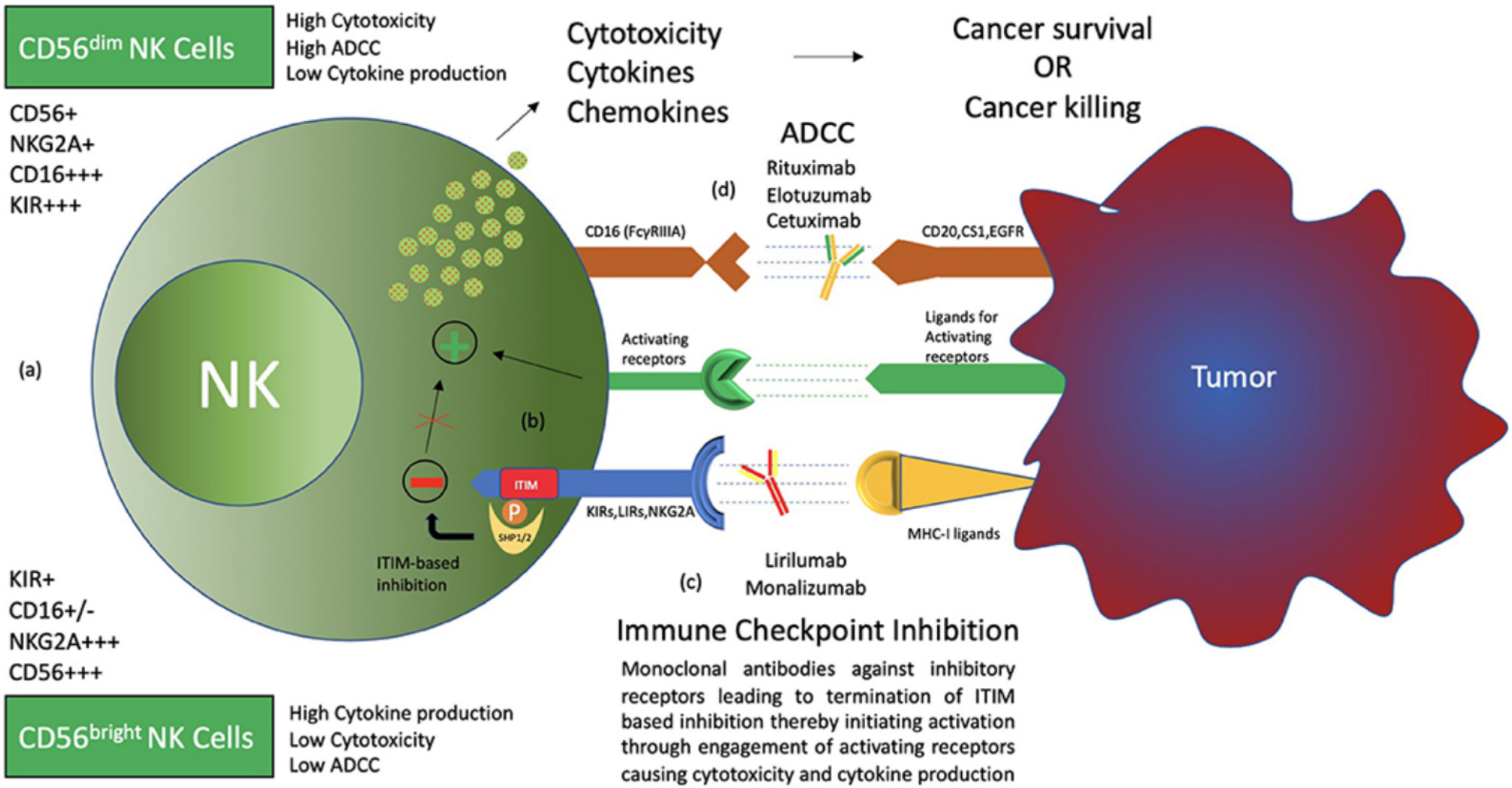
Immune check point in cancer

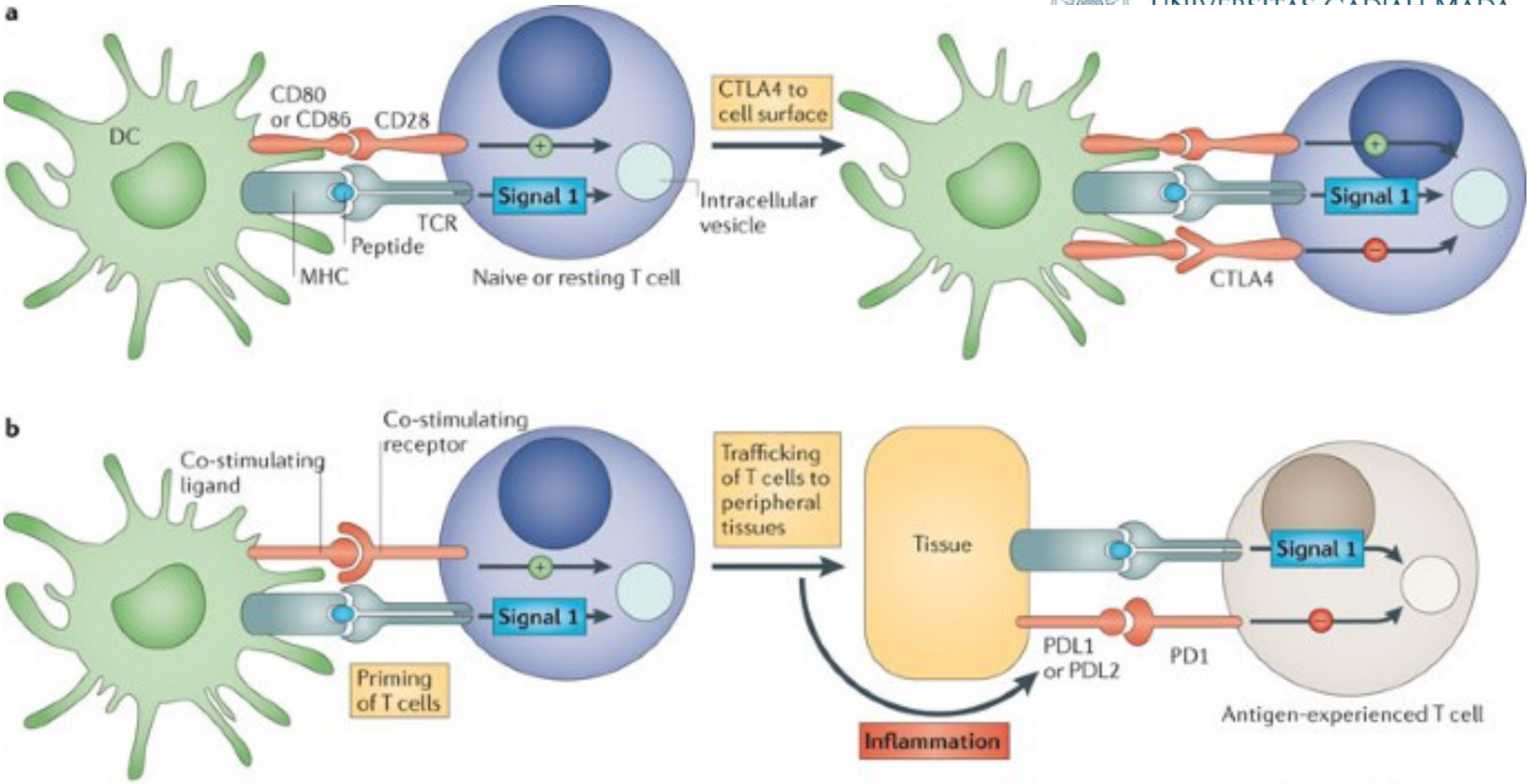


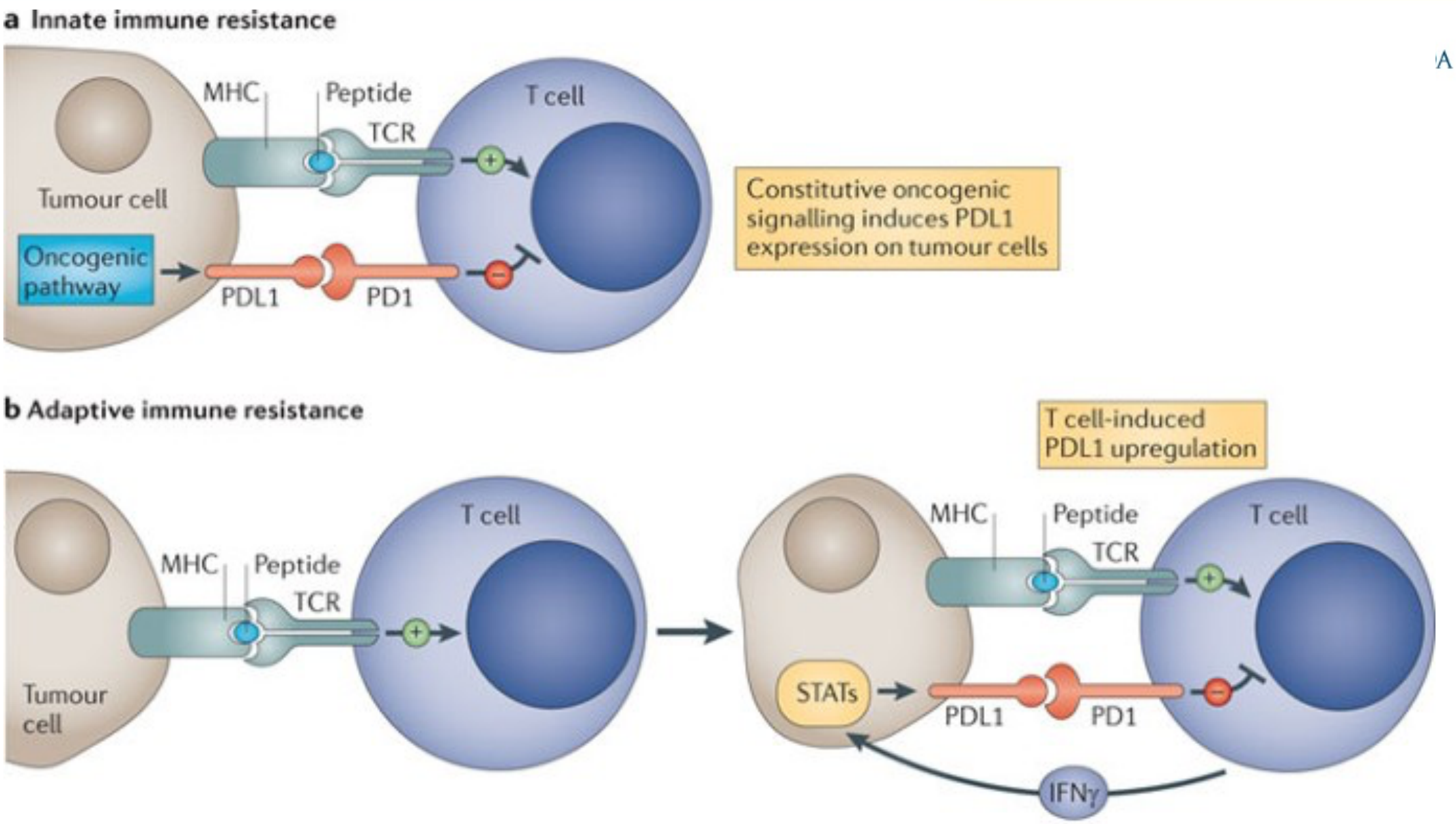
Immune check point in cancer



Immune check point in cancer




a
DC
CD80
or CD86
CD28
TCR
Peptide
MHC
Signal 1
Naive or resting T cell
CTLA4 to
cell surface
Intracellular
vesicle
Signal 1
CTLA4
b
Co-stimulating
ligand
Co-stimulating
receptor
Signal 1
Priming
of T cells
Trafficking
of T cells to
peripheral
tissues
Tissue
Signal 1
PDL1
or PDL2
PD1
Antigen-experienced T cell
Inflammation
Nature Reviews | Cancer



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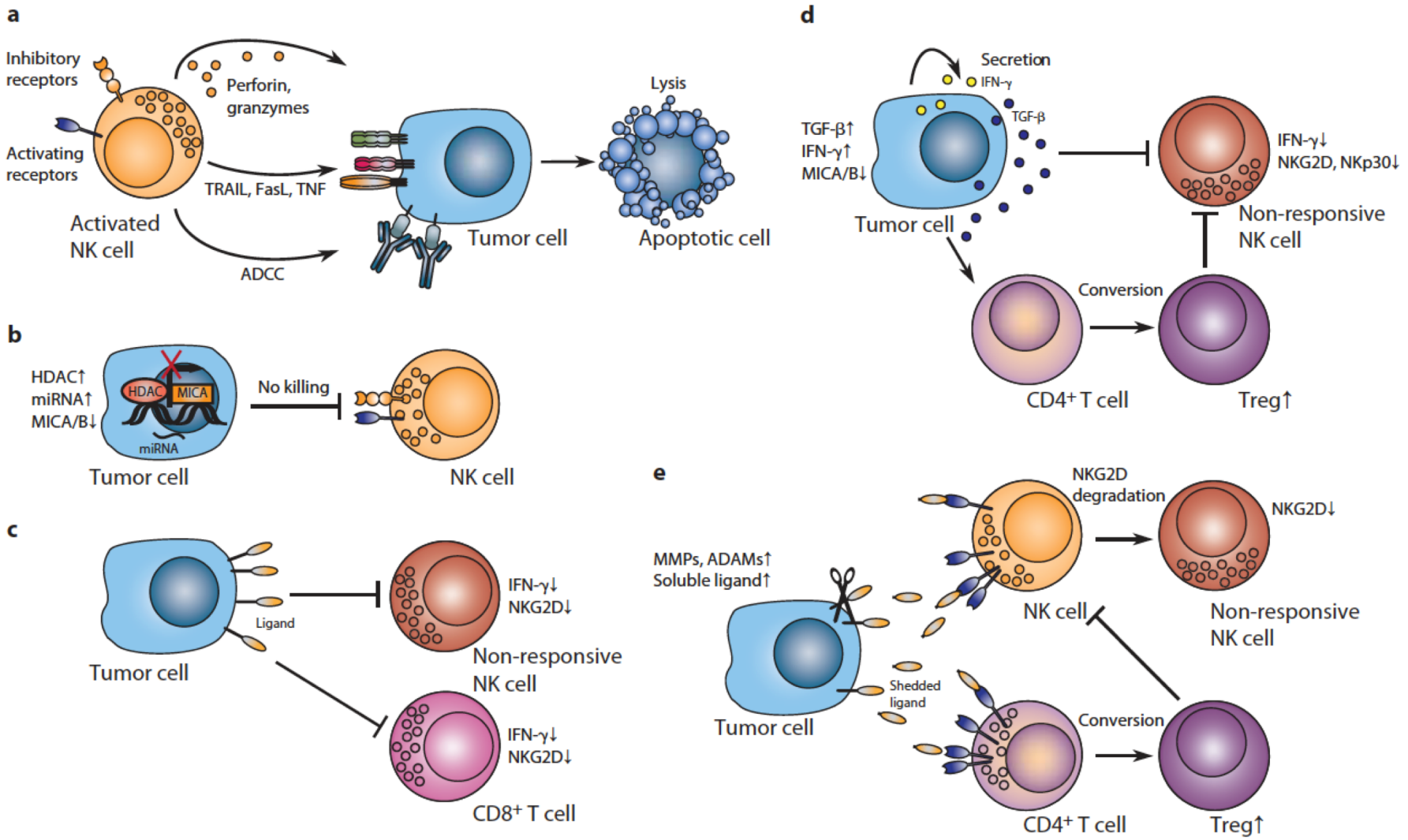
How does cancer evade the immune system?

How cancer avoiding the immune cells?

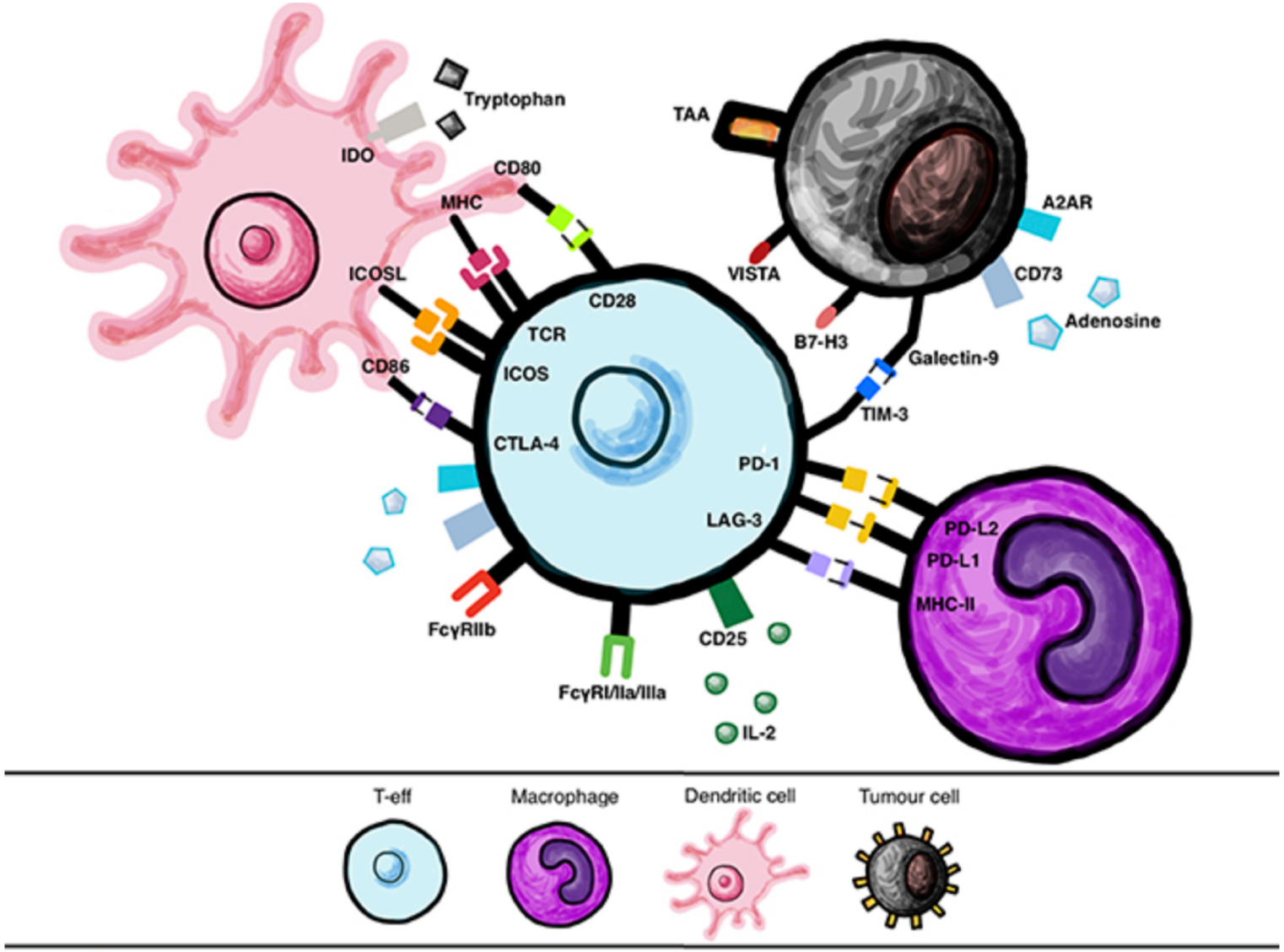
1. **Downmodulation of tumor antigen presentation** • Many tumor cells downregulate MHC class I molecules to avoid detection by cytotoxic CD8+ T cells.
2. **Changes within the tumor microenvironment** • The tumor microenvironment can produce cytokines that skew macrophages from a tumor-eliminating M1 phenotype to a tumor-promoting M2 phenotype.
3. **Tumors produce inhibitory molecules such as indolamine 2,3-dioxygenase (IDO)** to alter tryptophan catabolism and inhibit T cell responses. • Tumors secrete molecules involved in remodeling of the extracellular matris in the tumor microenvironment, making it difficult for immune cells to access the tumor.
4. Dysregulation of antigen presenting cells • Dendritic cells within the tumor microenvironment often have low levels of proinflammatory cytokine production, costimulatory molecules and MHC class II expression.
5. Induction of T cell tolerance • Immature DCs in the tumor microenvironment cannot fully activate T cells, and instead induce anergic T cells that are unable to eliminate the tumor.
6. Increased expression of co-inhibitory signals • Tumors can increase expression of ligands for the inhibitory receptors, CTLA-4 and PD-1, which bind to B7-1/B7-2 or PD-L1/PD-L2. This decreases the amplitude of the antigen-specific T cell response.
7. Induction of regulatory T cells • Tumors secrete cytokines such as TGF-beta that induce T regulatory (iTreg) cells which suppress antigen-specific T cells.

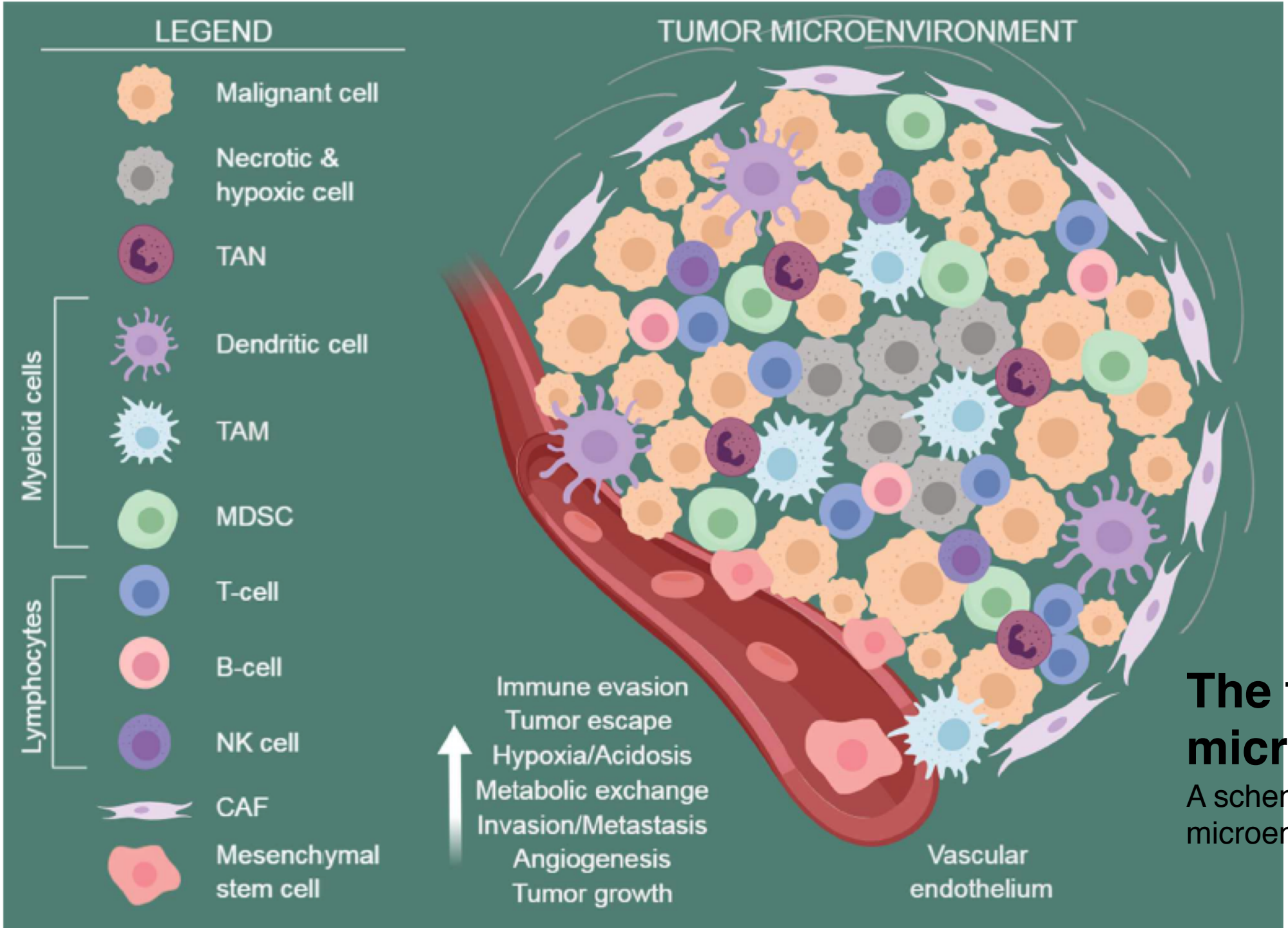
Strategies of tumor immune escape from NK cell-dependent immunosurveillance.



NK cell recognition is mediated by a fine-tuned balance of activating and inhibitory signals

indolamine 2,3-dioxygenase (IDO) inhibits T cells response





The tumor microenvironment.

A schematic view of the tumor microenvironment components

What are the types of immunotherapy?

- Immune checkpoints

- **Tumor-specific T cells** must discriminate between **destruction of the tumor cell** and **survival of the target cell**. Important for discrimination are proteins on both the T-cell and the target cell: CD8 is a T cell and the coreceptor for the T cell receptor (TCR).

- PD-L1 and PD-L2 (programmed cell death proteins) are transmembrane proteins that suppress the adaptive arm of the immune system. **PD-1** on the T-cell is activated by the cell surface ligands on the tumor cell. Upregulation of PD-L1 may allow cancers to evade the host immune system.

- TIM-3 is an inhibitory molecule that is induced following T cell activation. As a negative regulatory immune checkpoint,

- STING (stimulator of interferon genes) **is a key mediator of innate immunity**, and **involved in the induction of an anti-tumor immune response**.

Key regulators of the STING pathway are:

1. Interferon regulatory factors (**IRFs**) comprise a family of transcription factors that function within the Jak/Stat pathway to regulate interferon (IFN) and IFN-inducible gene expression in response to viral infection

2. STING is a signaling molecule associated with the endoplasmic reticulum (ER) and is essential for controlling the transcription of numerous host defense genes (including type I interferons (IFNs) and pro-inflammatory cytokines) following the recognition of aberrant DNA species or cyclic dinucleotides in the cytosol of the cell. Sting can translocate out of the ER upon activation.

Cancer treatments that use the immune system

Some cancer treatments use parts of the immune system to help treat cancer.

- **Immunotherapy :** Immunotherapy is a treatment for some types of cancer. It uses the immune system to find and kill cancer cells.
- **monoclonal antibodies (MABs)** which recognise and attack certain proteins on the surface of cancer cells
- **vaccines to help the immune system** to recognise and attack cancer
- **Cytokines** to help to boost the immune system
- **CAR T-cell therapy** (also called adoptive cell transfer) to change the genes in a person's white blood cells