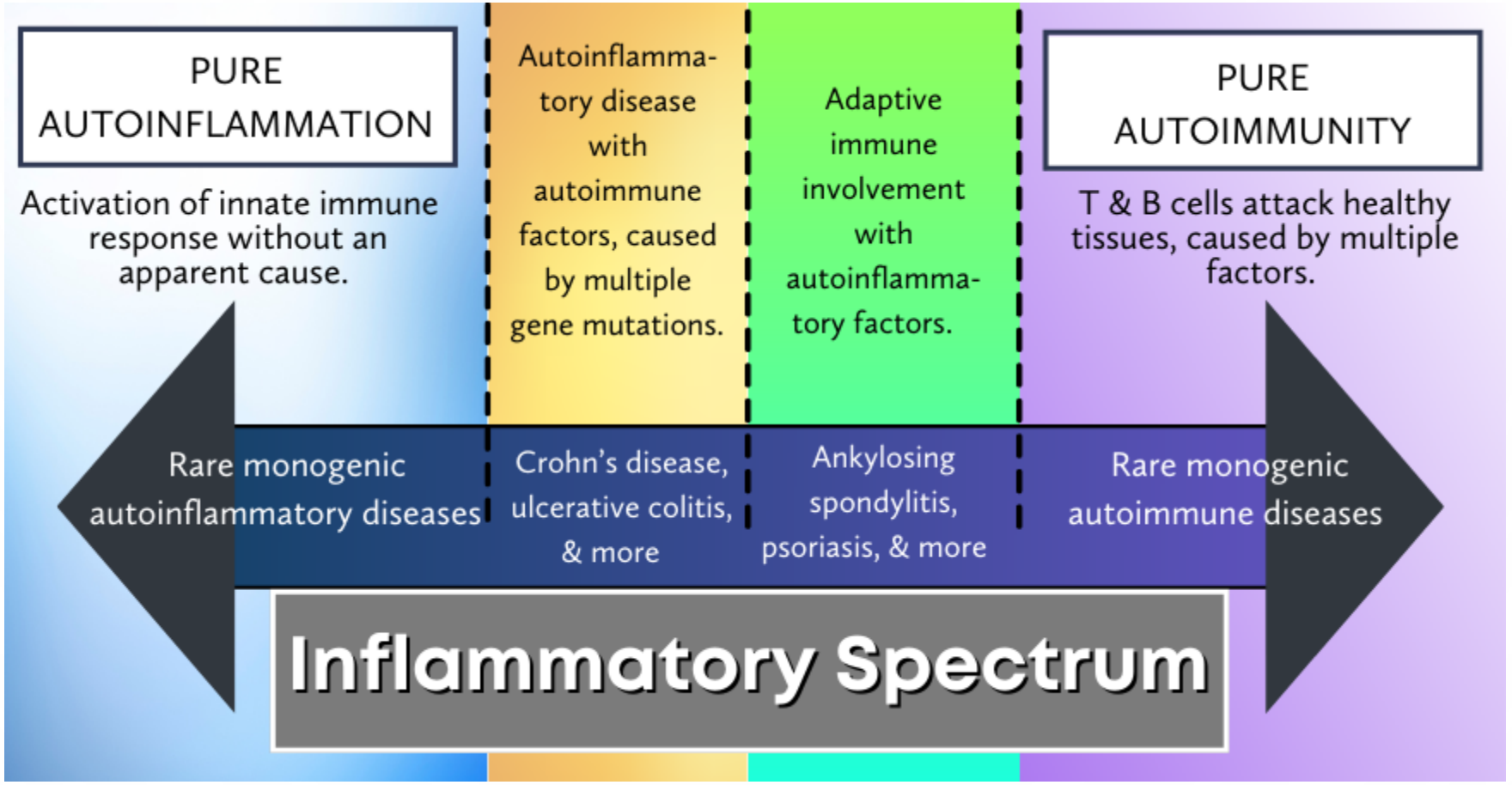
PART B

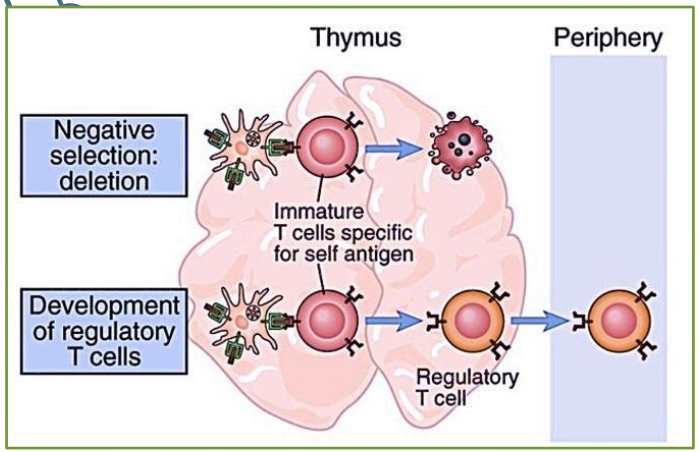
IMMUNE SYSTEM IN ACTION

- TYPICAL RESPONSE TO INFECTIONS (INTERACTIVE DISCUSSION IN CLASS)
- REGULATION OF IMMUNE RESPONSE (INTERACTIVE DISCUSSION IN CLASS)
- AUTO-IMMUNITY VS AUTO-INFLAMMATION
- TRANSPLANTATION: ACUTE GRAFT VERSUS HOST DISEASE (GVHD)
- IMMUNO-ONCOLOGY
- OSTEO-IMMUNOLOGY

IMMUNE SYSTEM IN ACTION
AUTO-IMMUNITY VS AUTO-INFLAMMATION



IMMUNE SYSTEM IN ACTION
AUTOIMMUNITY

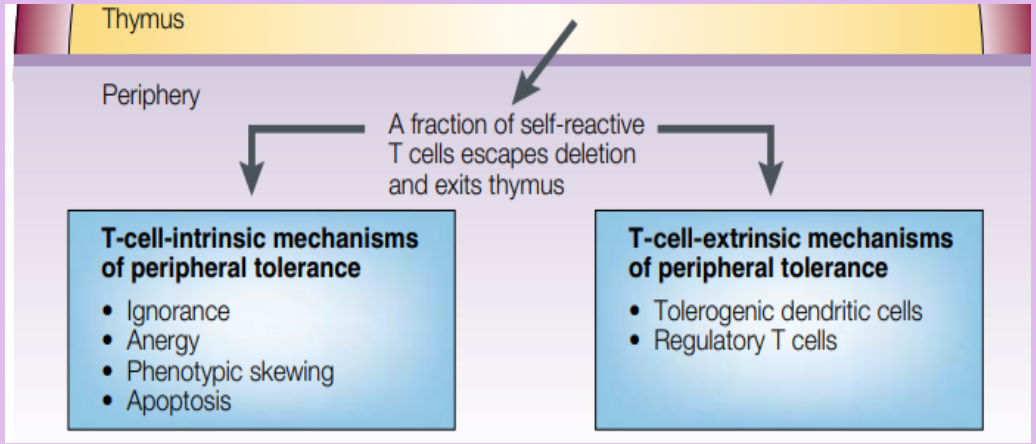


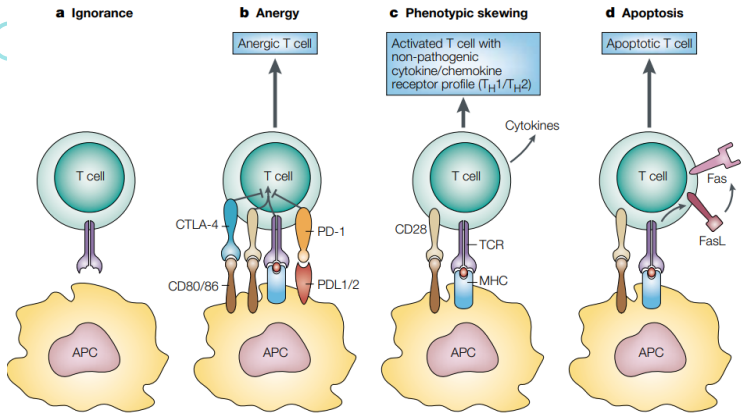
Basic Mechanisms of Self-tolerance:

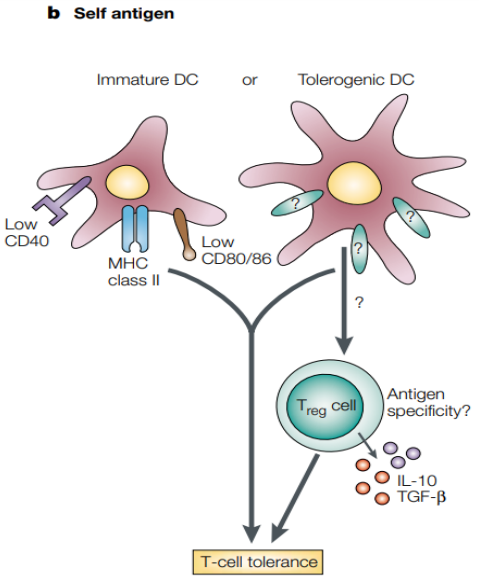
- **Central Mechanisms** (within **Thymus**):
  - Negative Selection: elimination of strongly self-reacting T-cells by not providing surviving signals and induction of apoptosis
  - Central induction of T regulatory program in T-cells with moderate self-reactivity

But since the thymic microenvironment does not express the total possible repertoire of self-antigens it is always the possible that T cell with self-reactivity may escape from thymus. Thus, mechanism to control or eliminate these cells in the periphery are required

- **Peripheral Mechanisms** (in tissues and lymphoid organs):



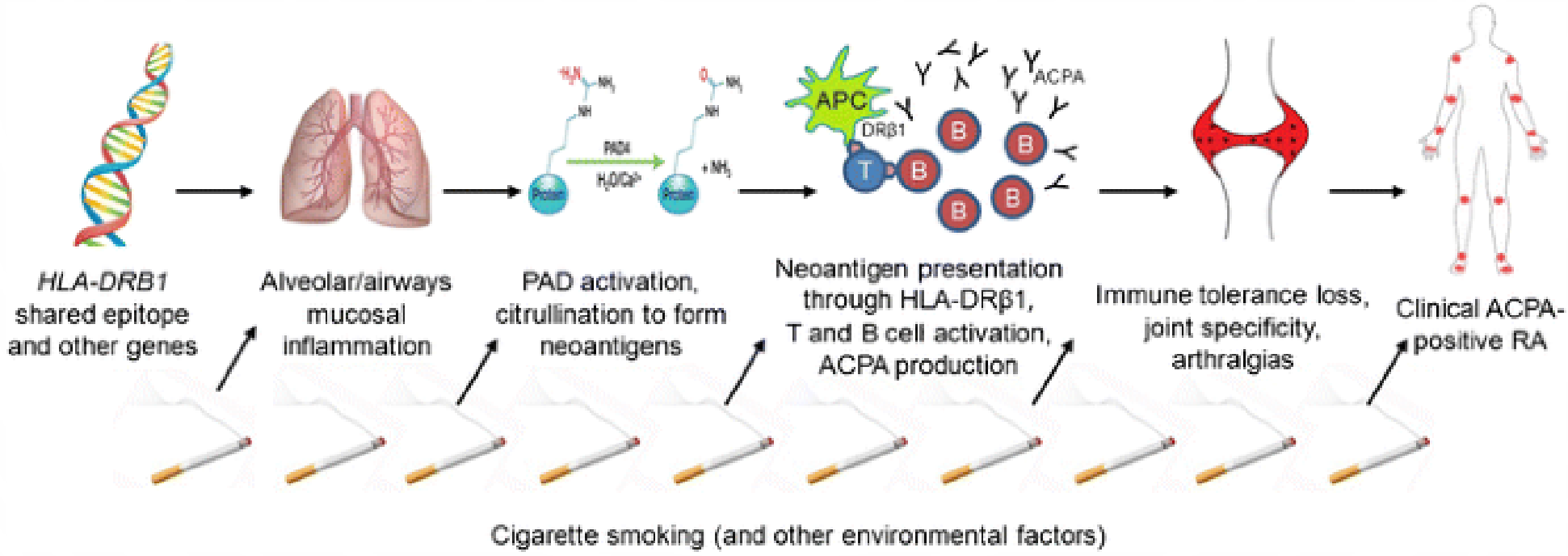




IMMUNE SYSTEM IN ACTION

MECHANISM OF AUTO-IMMUNITY

NEO-EPITOPES VIA POST-TRANSLATIONAL MODIFICATIONS: THE EXAMPLE OF CITRULLINATION IN RHEUMATOID ARTHRITIS



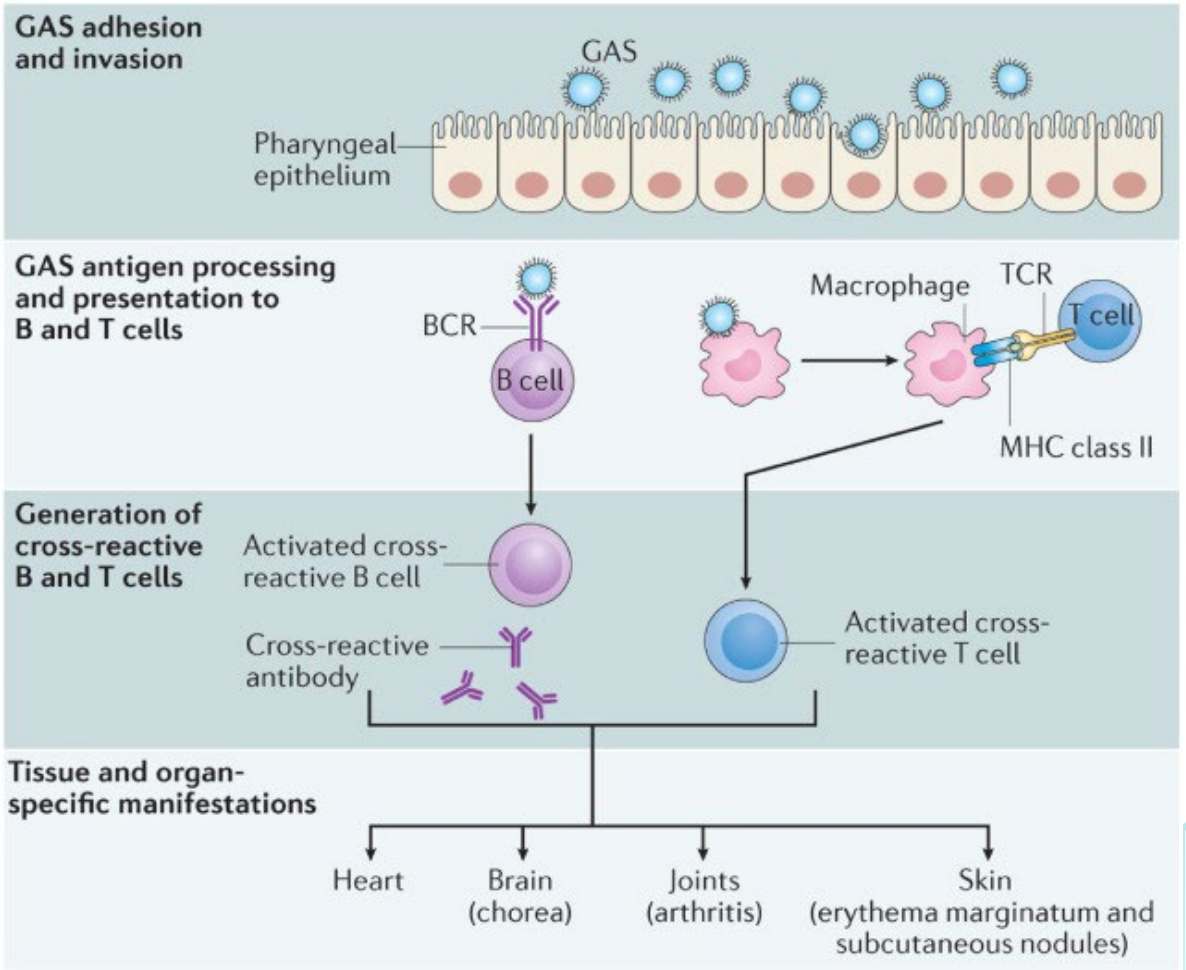
IMMUNE SYSTEM IN ACTION
MECHANISM OF AUTO-IMMUNITY
MOLECULAR MIMICRY: THE EXAMPLE OF ACUTE RHEUMATIC FEVER

Acute Rheumatic fever follows infection with **Group A *Streptococcus*** (GAS)

Multi-organ inflammatory disorder affecting:

- Heart (carditis)
- Joints (arthritis)
- Brain (Sydenham's chorea)
- Skin (erythema marginatum)
- Subcutaneous tissues (nodules)

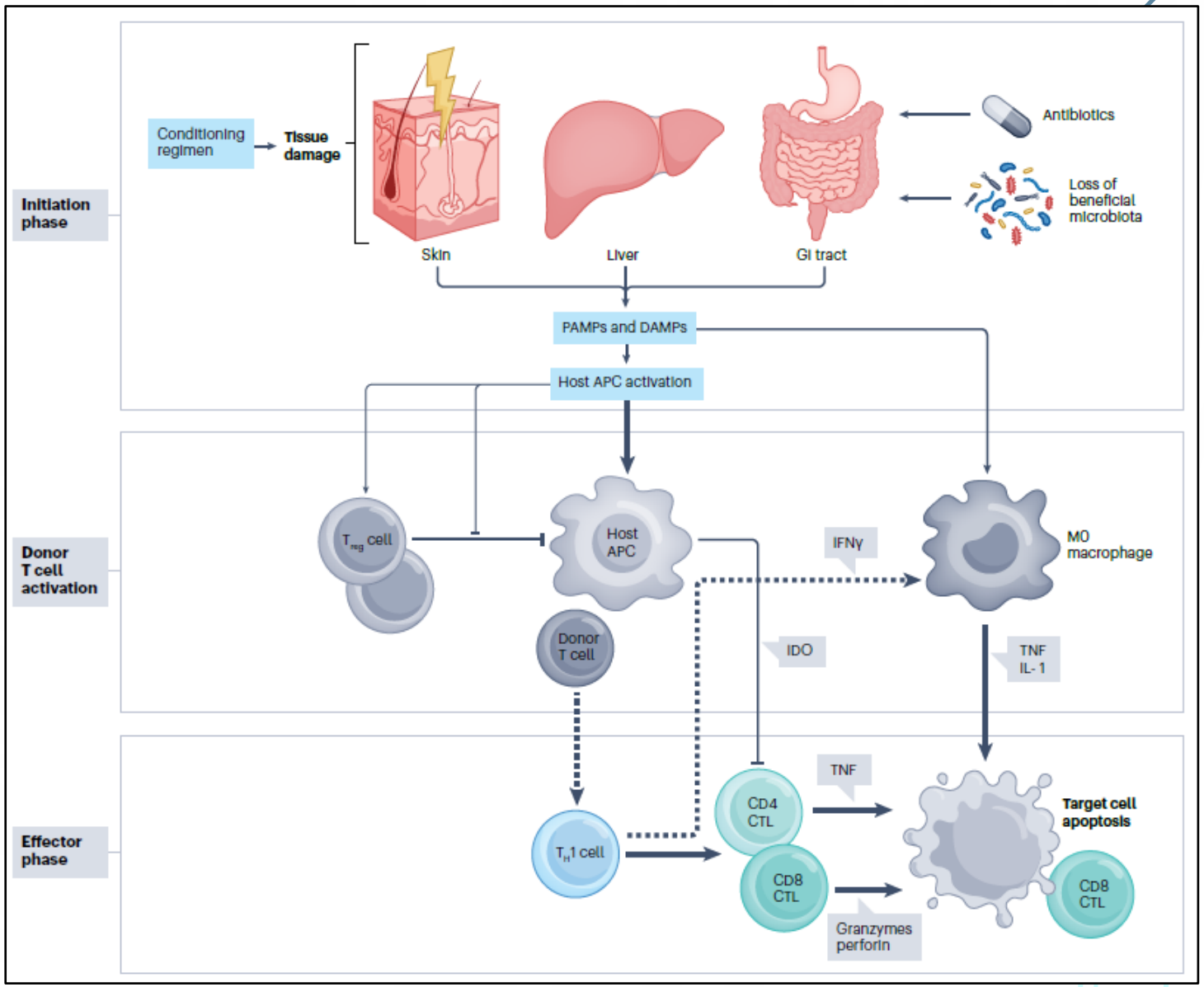
Underlying mechanism: antigens from GAS share sequence or structural similarities with self-antigens (**Molecular Mimicry**)



IMMUNE SYSTEM IN ACTION
GRAFT VERSUS HOST DISEASE (GVHD)

GVHD:

- Occurs after allogeneic hematopoietic cell transplantation (alloHCT)
- Key risk factor: HLA disparity
- Recognition & Destruction of recipient tissues by donor immunocompitent cells
- Classic involvement:
  - Skin
  - Gastrointestinal tract (vomiting, diarrhea)
  - Liver (increase bilirubin/jaundice)
- Treatment:
  - Routine use of conditioning & prophylactic treatment
  - 1st line: steroids
  - 2nd line: ruxolitinib (JAK2i)
  - 3rd line: TNFi, MMF etc

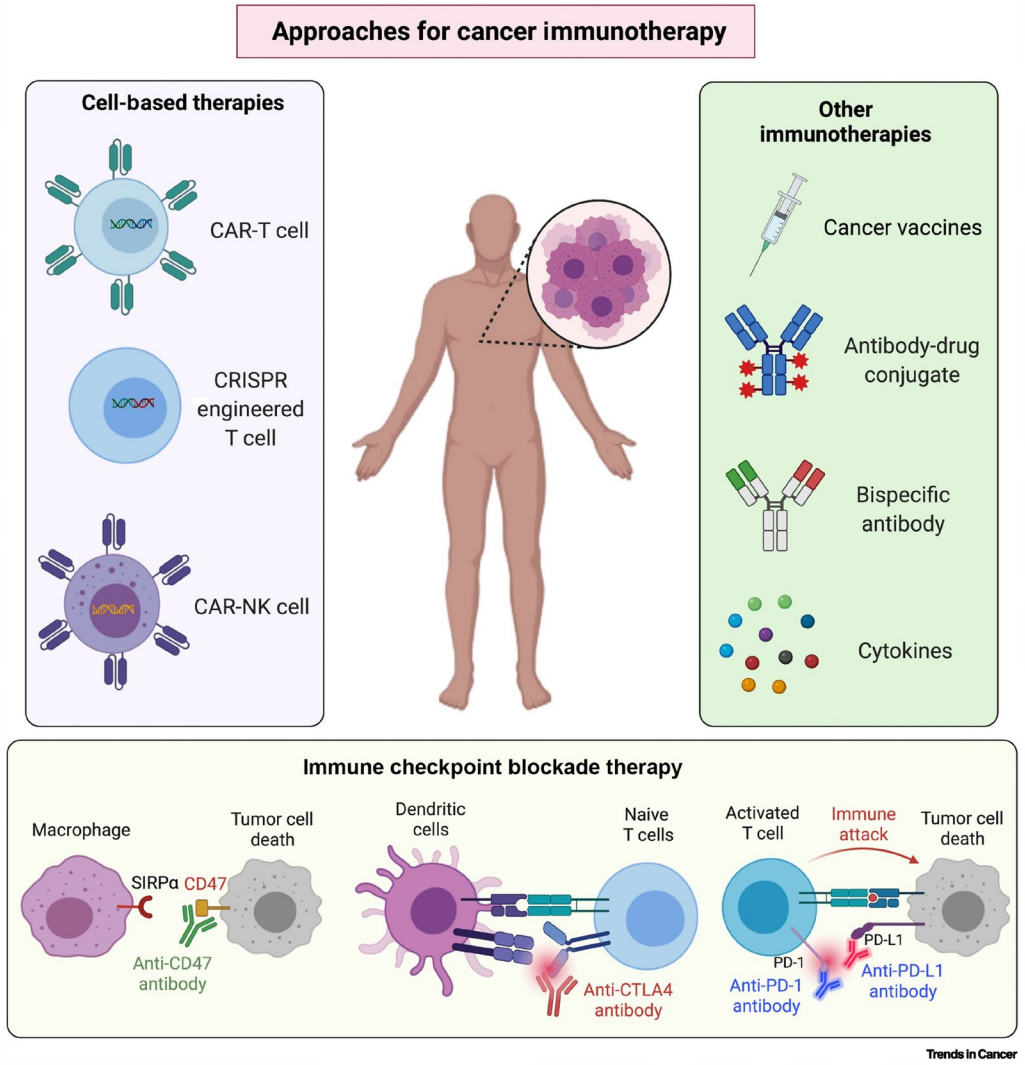


CANCER IMMUNOLOGY

EMERGENCE OF **IMMUNOTHERAPY** AS A NEW PILLAR IN CANCER TREATMENT

Treatment Modalities for Cancer:

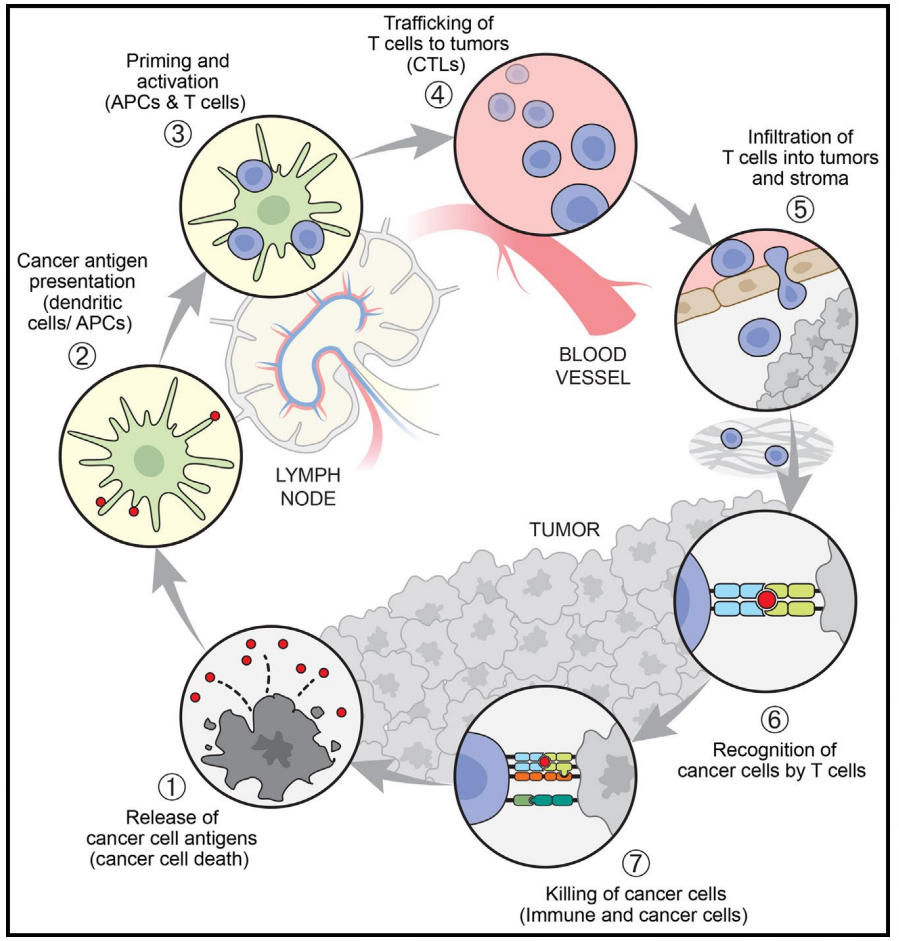
1. Surgery
2. Radiation
3. Chemotherapy
4. Small Molecules
   (e.g., Tyrosine-Kinase Inhibitors)
5. **Immunotherapy**



CANCER IMMUNOLOGY
IMMUNOSURVEILLANCE AGAINST TUMORS:
TUMORS ELICIT **IMMUNOGENIC NEO-ANTIGENS**

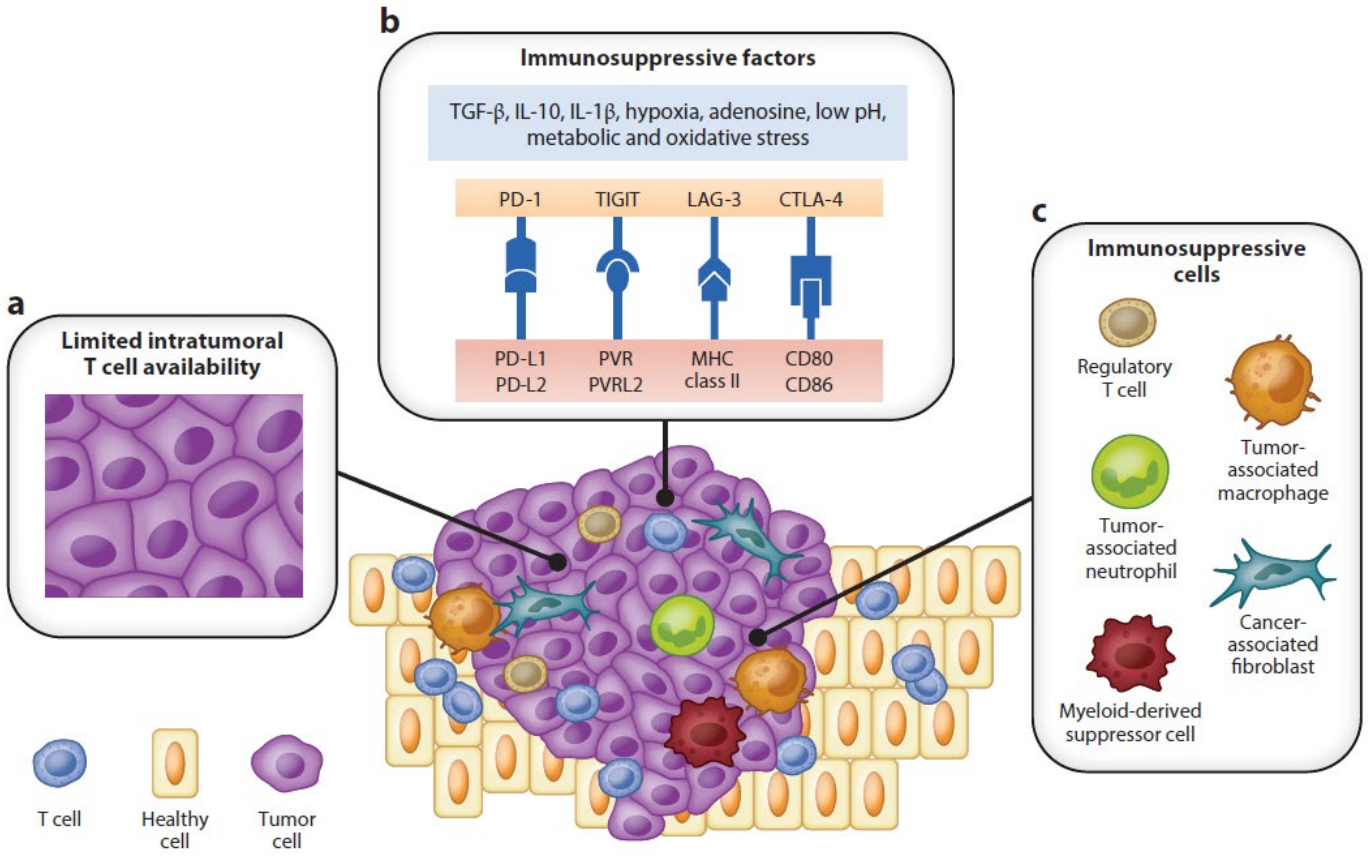
Tumor-cell Mutagenesis is one mechanism of **neo-antigen generation** that triggers **cytotoxic immune response** against tumor cells

Then,
-why we develop cancer?
-how tumor cells **escape** immune surveillance?



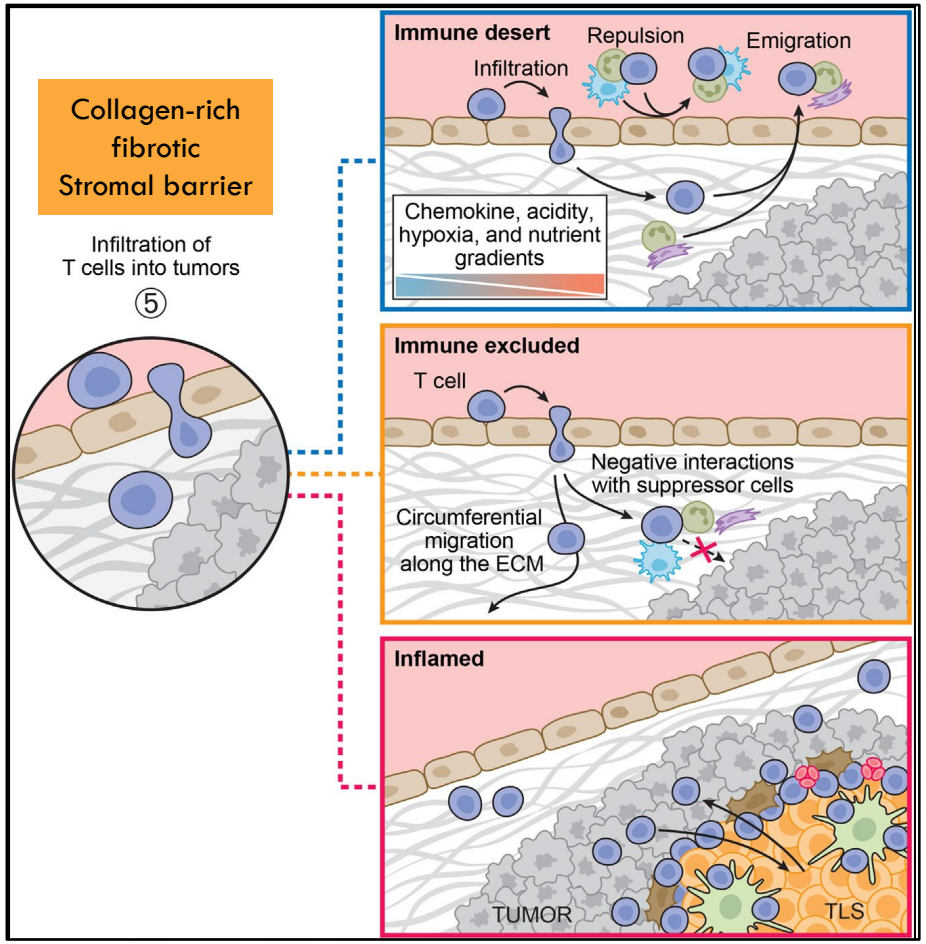
Mellman I, et al, Immunity 56, 2023

CANCER IMMUNOLOGY
HOW TUMORS ESCAPE IMMUNOSURVEILLANCE: THE ROLE OF **TUMOR MICROENVIRONMENT**



Annu. Rev. Cancer Biol. 2022. 6:17–34

CANCER IMMUNOLOGY
HOW TUMORS ESCAPE IMMUNOSURVEILLANCE:
LIMITED INTRA-TUMOR T-CELL AVAILABILITY



Mellman I, et al, Immunity 56, 2023

3 Cancer immunotypes based on Intra-tumor T-cell availability	
Cancer Immunotypes	**Definition**
Immune Inflamed **e.g., Melanoma**	Abundant **T-cells** infiltrating the **tumor parenchyma**
Immune Excluded **e.g., Colon Ca**	T-cells infiltrating **stroma**, but excluded from tumor parenchyma
Immune Desert **e.g., Prostate Ca**	No immune infiltrate

CANCER IMMUNOTHERAPIES

HOW TUMORS ESCAPE IMMUNOSURVEILLANCE:

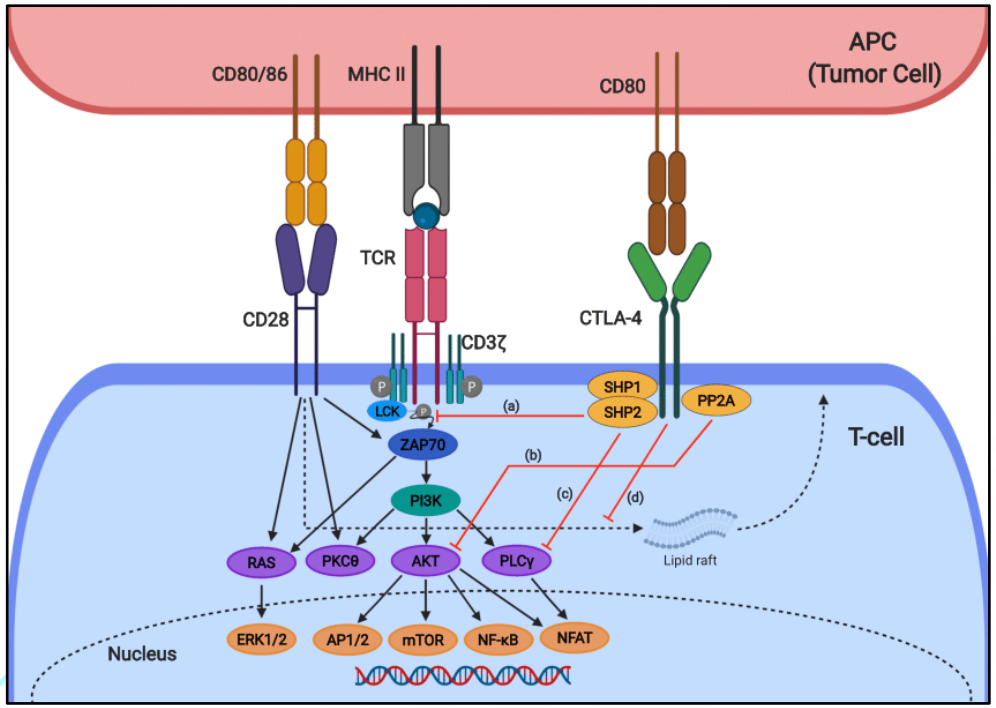
LOCAL IMMUNOSUPPRESSION BY THE TUMOR MICROENVIRONMENT

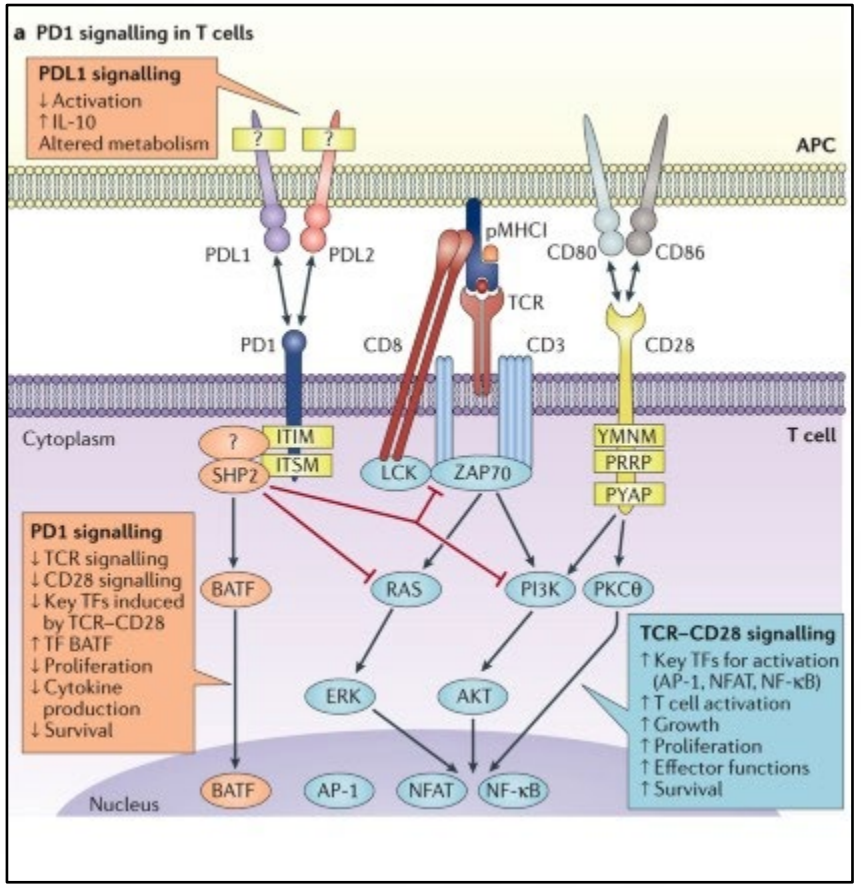
CHECK POINTS OF T-CELL ACTIVATION:

CTLA4 & **PD1** (**LAG3,** TIGIT) EXPRESSED ON T-CELLS & **PDL1/PDL2** EXPRESSED ON TUMOR CELLS/STROMA
ATTENUATE AG-MEDIATED T-CELL ACTIVATION WITHIN TUMOR MICROENVIRONMENT

CTLA4:

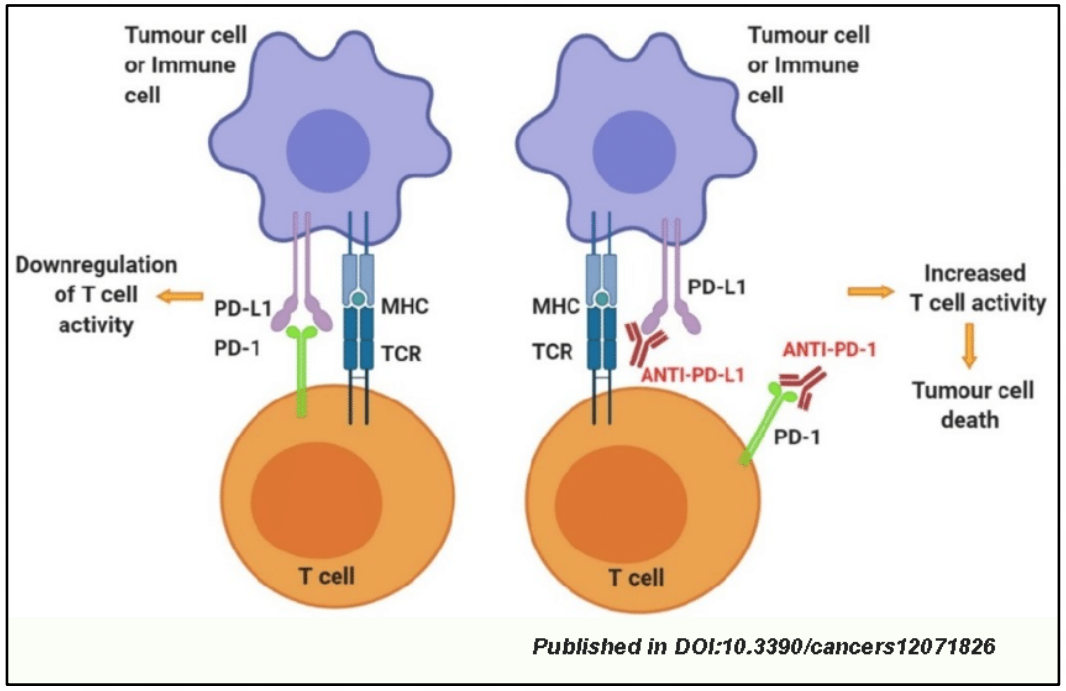
1) competes with CD28 for signal 2 mediating CD80/86
2) Induces trans endocytosis of CD80/86 reducing signal 2 levels
3) inhibits TCR signaling



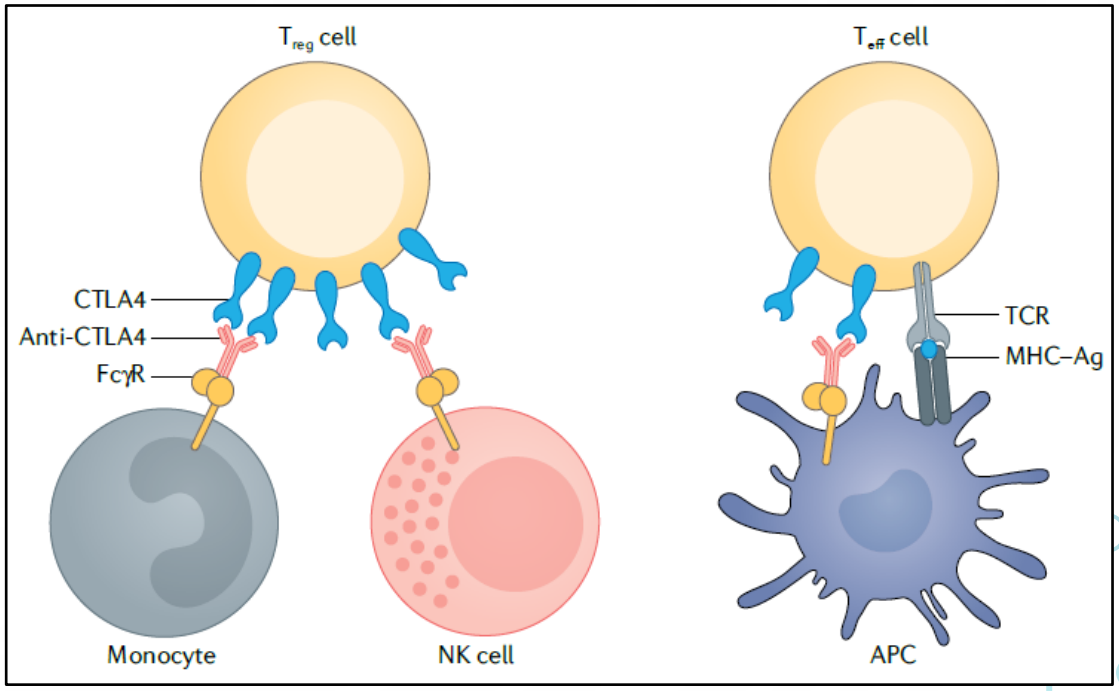


NEW CLASS CANCER IMMUNOTHERAPIES CHECK-POINT INHIBITORS: REVERSE T-CELL EXHAUSTION

anti-PD-1 & anti-PD-L1



anti-CTLA4



Additional Check-point inhibitors: anti-LAG3 (approved), anti-TIGID (in late development)

CANCER IMMUNOTHERAPIES
T-CELL (OR NK-CELL) ENGAGERS:

BI-SPECIFIC ANTIBODIES SIMULTANEOUSLY ENGAGING CD3 ON T-CELLS AND AN ANTIGEN ON TUMOR CELLS

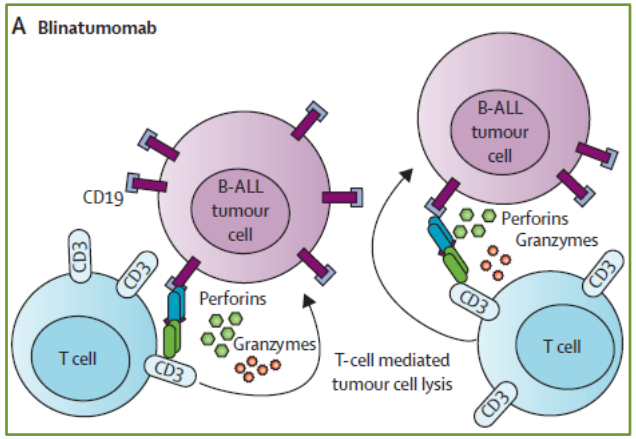
Basic Principle:

Simultaneous binding to antigens on tumor cells (e.g., CD19, CD20, BCMA, GPRC5D) and to CD3 on T-cells (or CD16 on NK-cells) results in recruitment of T cells (or NK-cells) to the tumor, followed by T-cell (or NK-cell) activation, degranulation of cytotoxic mediators and tumor cell elimination.

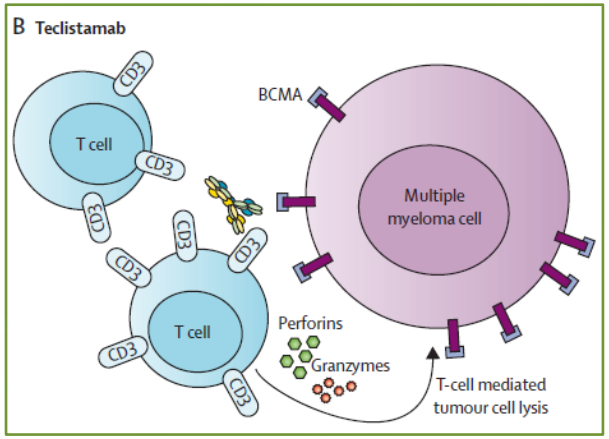
Challenges:

- Resistance mechanisms
- Less effective in solid tumors compared to hematologic malignancies
- Side-effects: Cytokine-release syndrome, Tumor-lysis syndrome, Infection due to T-cell exhaustion

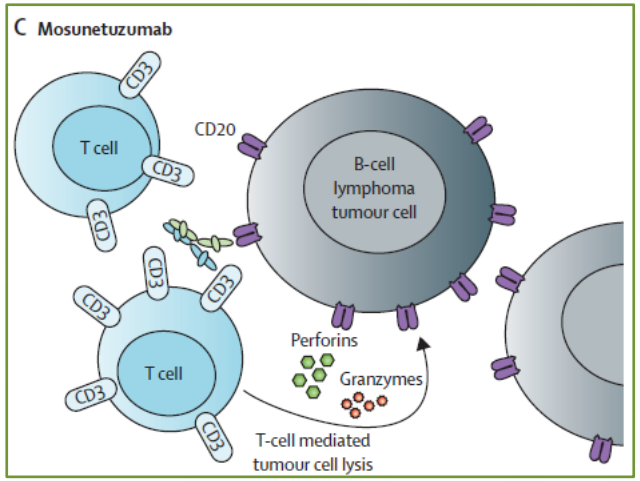
CD3XCD19



CD3XBCMA



CD3XCD20



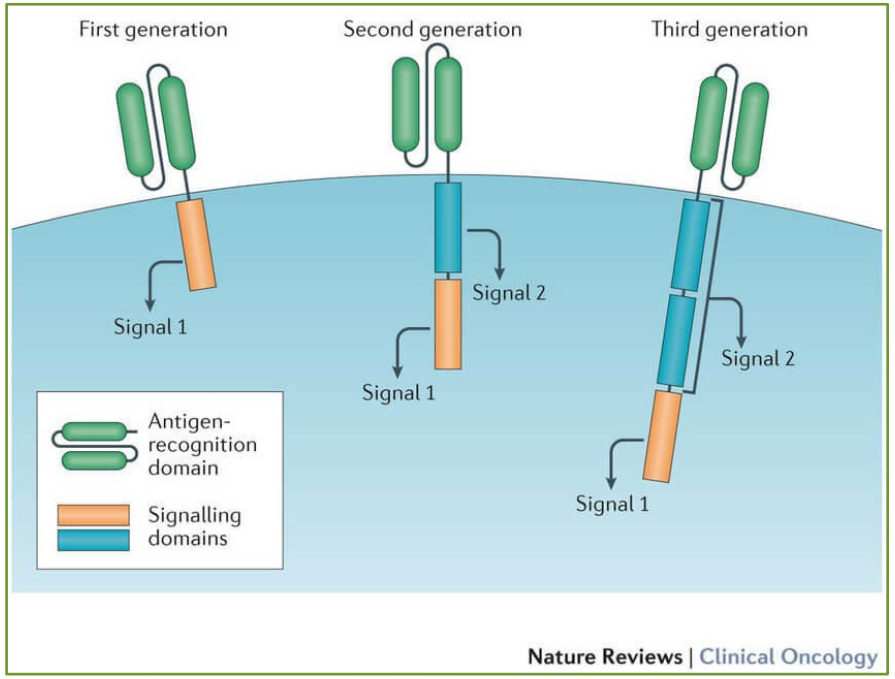
Lancet 2023; 402: 142–58

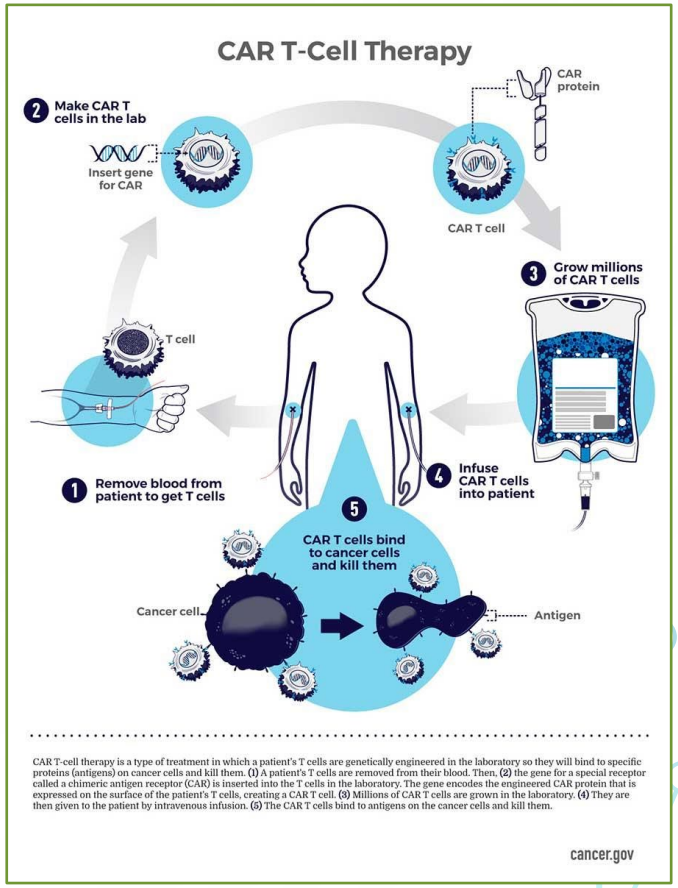
CANCER IMMUNOTHERAPIES
CHIMERIC ANTIGEN RECEPTOR THERAPIES
CAR-T & CAR-NK THERAPIES

Basic Principle:

- Chimeric Antigen Receptors (CARs) are synthetic fusion proteins comprising:
  - ❑ an **extracellular antigen-recognition domain** (e.g., the single-chain variable fragment (scFv) of an antibody)
  - ❑ **intracellular signaling moieties that trigger cell activation** (e.g., CD28, 4-1BB, CD3ζ chain)

- CARs **can be expressed on immune effector cells (T-cells or NK-cells)** for the purpose of reprogramming their specificity to a particular target
  - ❑ CAR-T
  - ❑ CAR-NK

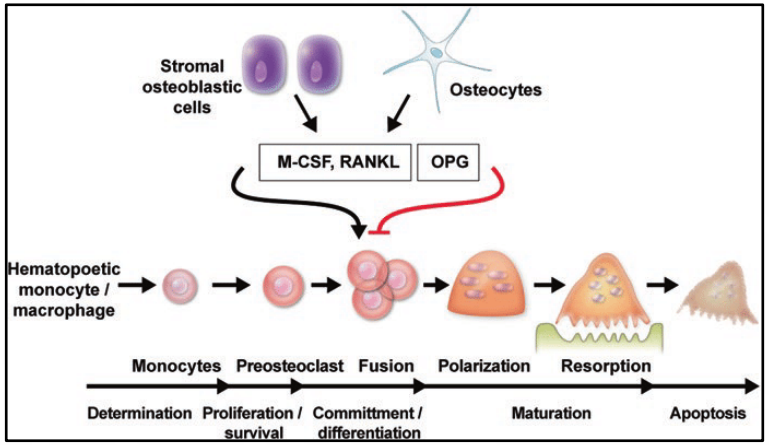




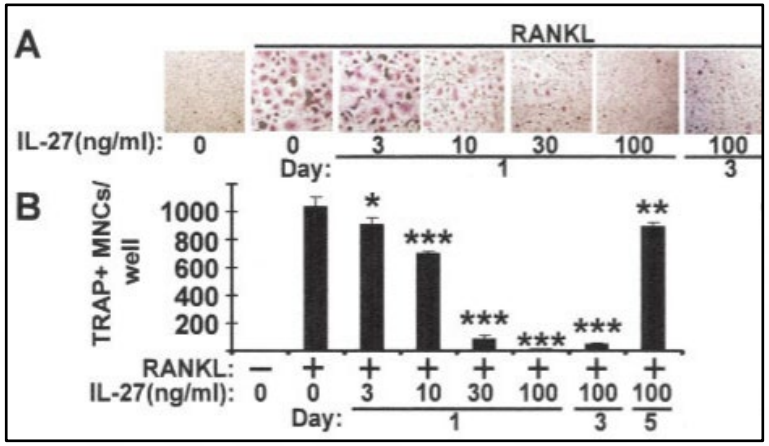
IMMUNE SYSTEM IN ACTION

OSTEOIMMUNOLOGY:
INTERPLAY BETWEEN BONE & IMMUNE SYSTEM

Immune cells: Osteoclast progenitors



Cytokines: Regulate Osteoclastogenesis



Kalliolias et.al., ARTHRITIS & RHEUMATISM 2010, 62, 402–413

Auto-Antibodies (ACPAs) & Cytokines induce bone destruction in Rheumatoid Arthritis