



Immunotherapy for Gynecologic Cancers

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Disclosures

- AstraZeneca – speakers bureau, consultant/advisory board
- GSK - speakers bureau, consultant/advisory board
- Eisai - consultant/advisory board
- MedLogix – consultant

Overview

- **Immunotherapy 101**
 - Immune system overview
 - Types of Immunotherapy
- **Role in Gynecologic malignancies**
 - Endometrial Cancer
 - Cervical Cancer
 - Ovarian Cancer

What is immunotherapy?

- **Definition**

- A treatment that uses the body's immune system to fight cancer

- **How it Works**

- Enhances the immune response against cancer cells
- Can target specific markers on tumor cells

IMMUNITY

INNATE IMMUNITY

Physical Barriers



Chemical Barriers



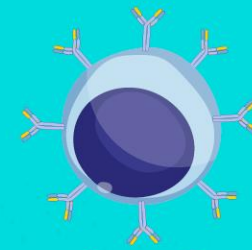
Cellular Defences



NK cells
Macrophages
Dendritic cells

ADAPTIVE IMMUNITY

Active Immunity



B cells
T cells

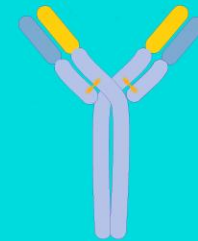
Natural



Vaccination



Passive Immunity



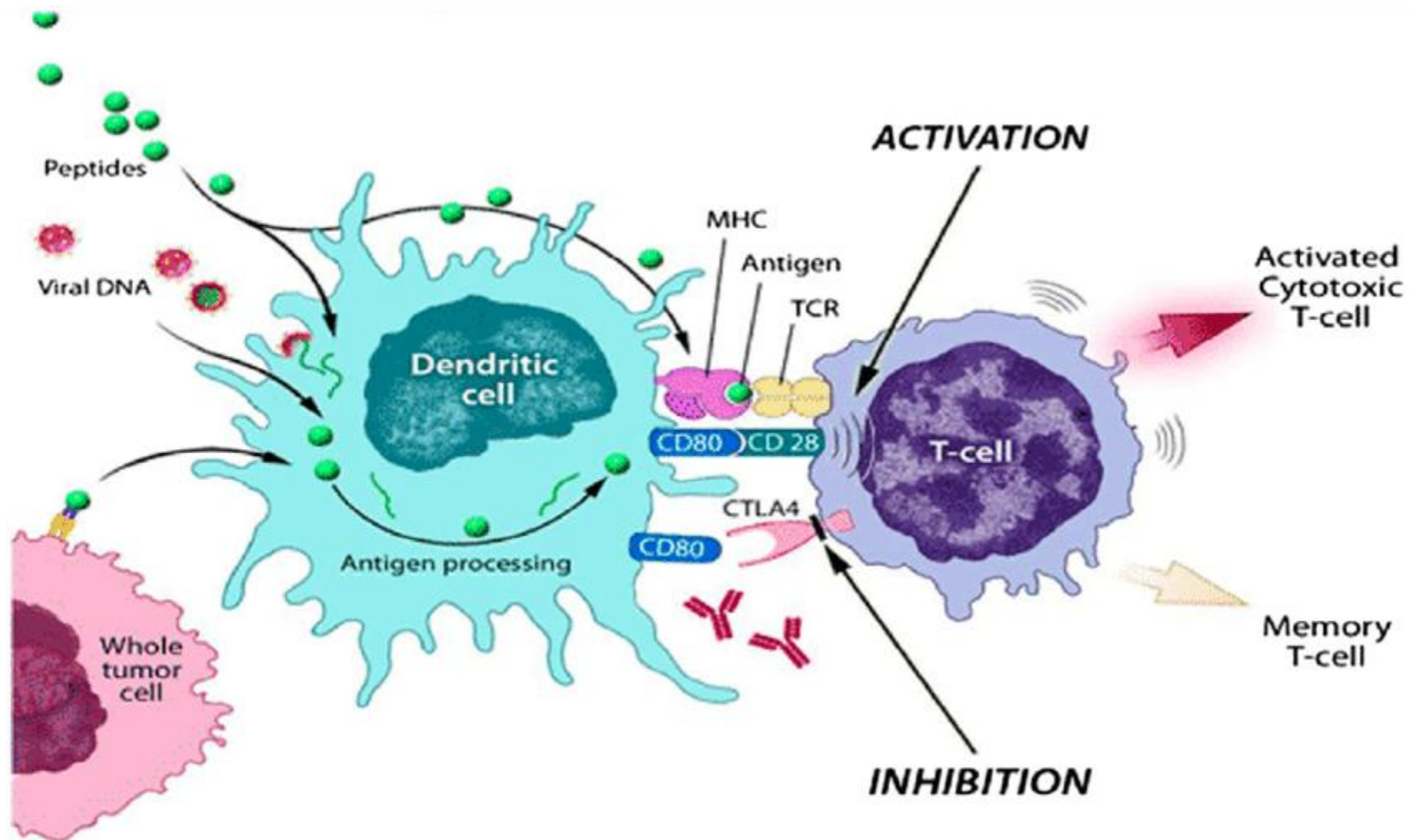
Maternal



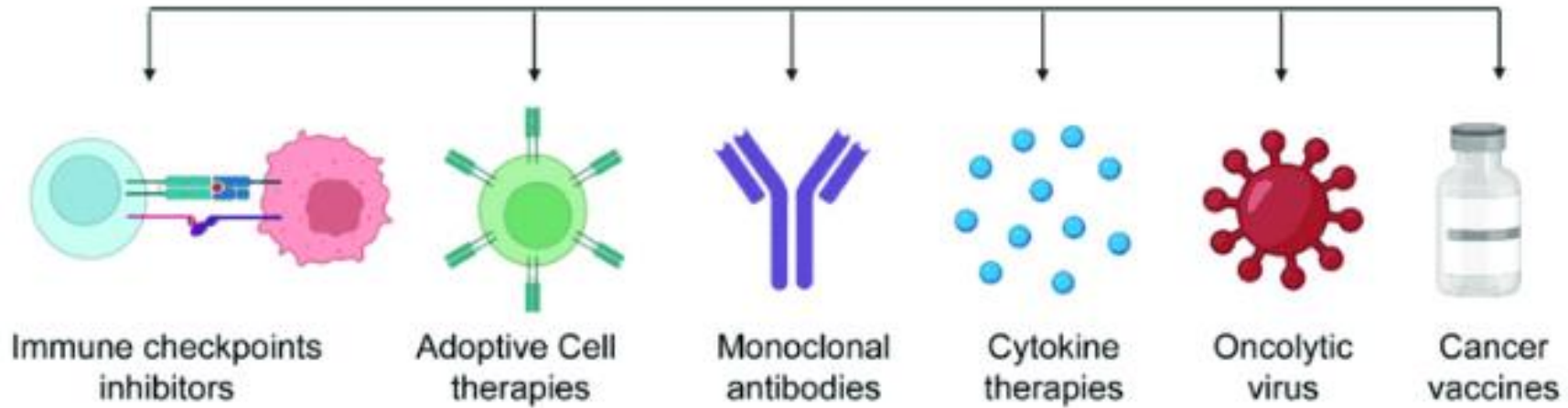
Artificial



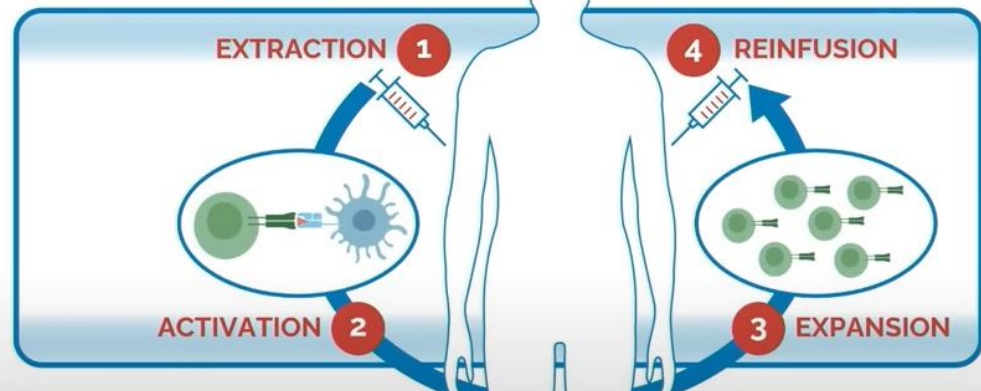
Interplay between Innate and Adaptive Immunity



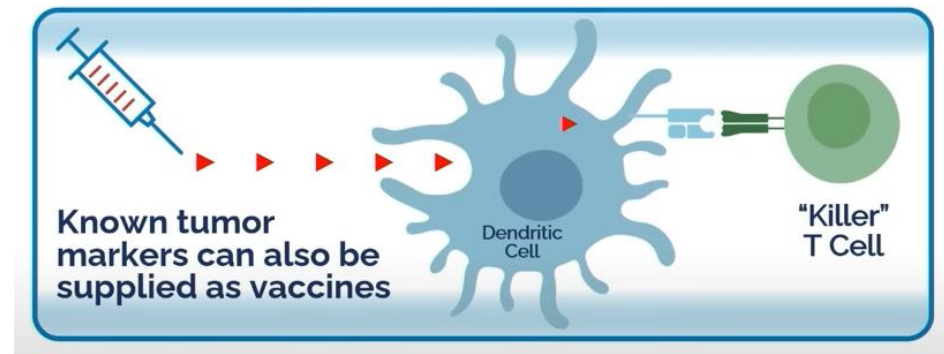
Types of Cancer Immunotherapy



Cell Therapy (CAR)T cell

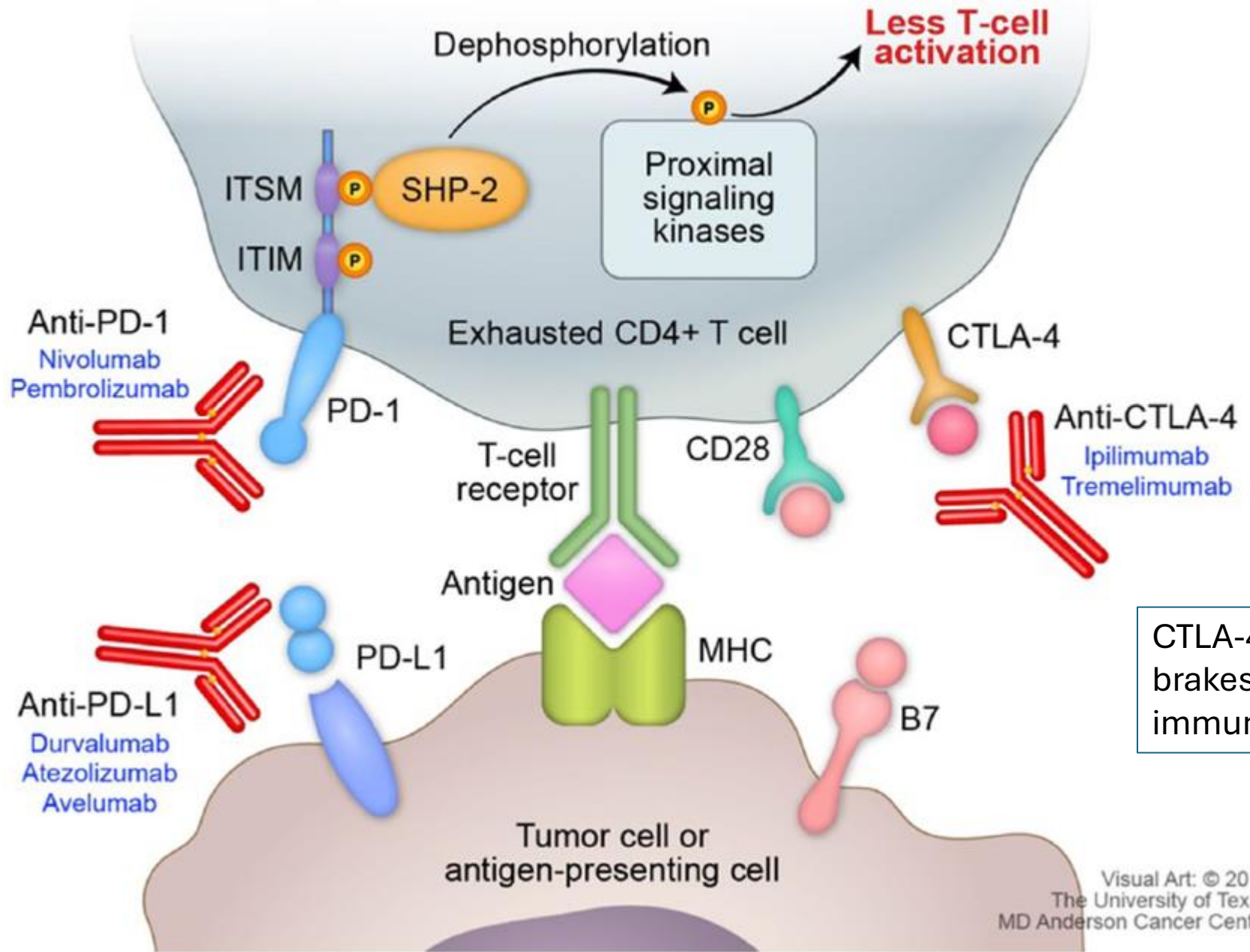


Vaccines



Immune Checkpoint Inhibitors (ICI)

Cancer cells use the PD-1 pathway to hide from T cells



CTLA-4 acts as the brakes on the immune system

Understanding personalized treatment

- Mutations and genomic instability
- Leads to changes that can alert immune system and affect response
- Tumor Genome stability and mutations
 - MSI-high
 - TMB
 - PDL1- expression
 - CPS score (≥ 1)



Endometrial Cancer – ICI with chemotherapy

dMMR

- Approximately 30% of cases
 - Dostarlimab
 - Pembrolizumab
 - Durvalumab
- Approximately 60-70% decreased risk of progression

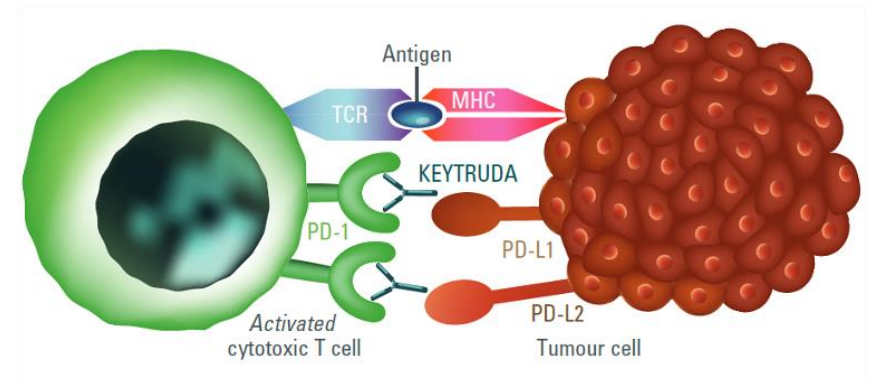
pMMR

- Approximately 70% of cases
 - Dostarlimab
 - Pembrolizumab
- 35-45% decreased risk of progression

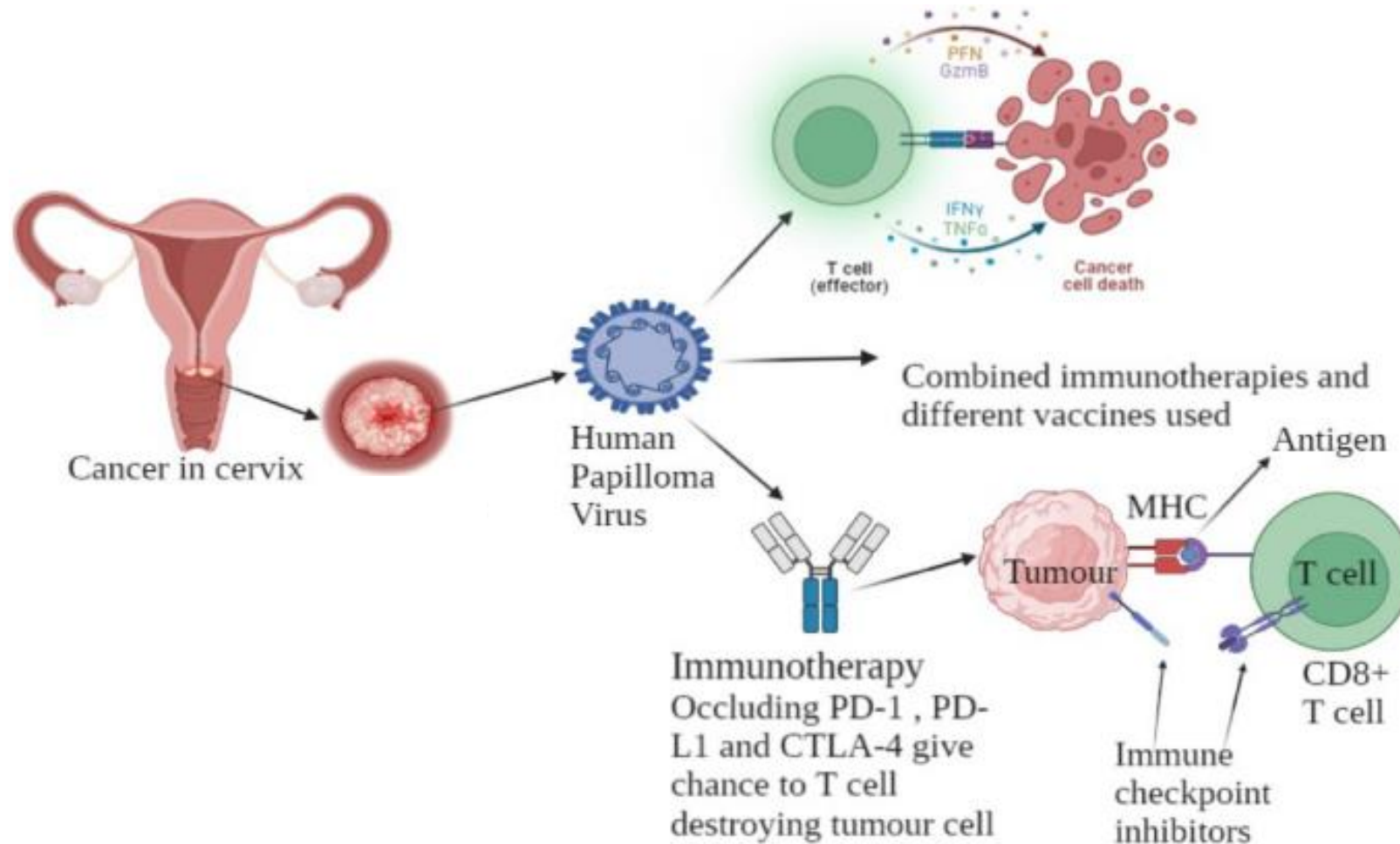
Approved with carboplatin and paclitaxel for all recurrent/metastatic tumors

Endometrial cancer – combination ICI

- Recurrent disease
- Pembrolizumab with Lenvatinib
 - Lenvatinib – oral multi TKI
 - Side effects: GI, fatigue, high blood pressure
- Improved responses over second line chemo



Immunotherapy Approaches in Cervical Cancer



Immunotherapy in Cervical Cancer

- **Upfront for FIGO 2014 stage III-IVA (PD-L1-positive (CPS \geq 1))**
 - Pembrolizumab with cisplatin and radiation
 - ~ 40% improvement in outcomes by adding pembro
- **Recurrent/metastatic disease (PD-L1-positive (CPS \geq 1))**
 - Pembrolizumab with platinum and taxane based chemo with or without bevacizumab
 - ~ 35% improvement in outcomes by adding pembro
 - Atezolizumab Pembrolizumab with platinum, taxane, and bevacizumab*
- **Recurrent/metastatic, progression after chemo**
 - Pembrolizumab alone
 - PD-L1-positive tumors (CPS \geq 1)
 - Cemiplimab and nivolumab have shown benefits*

*not yet FDA approved for this indication

KEYNOTE-A18
KEYNOTE-826
KEYNOTE-028

Ovarian Cancer and Immunotherapy – Why (Usually) Not?

- **ICI have shown relatively modest response (10-15%)**
- **Resistance related to:**
 - Lack of significant anti tumor T cell response
 - OC heterogeneity
 - Immune suppression in tumor microenvironment
 - High TMB and high MSI are rare in ovarian cancer

When do we use Immunotherapy in ovarian cancer?

- **Exception – dMMR or MSI**

- KEYNOTE 158 – RR 33% In 15 OVCA patients that are dMMR

- **In combination with other drugs**

- Oral cyclophosphamide, pembrolizumab, and bevacizumab
 - 75% of patients were platinum resistant
 - ORR 47.5%, clinical benefit in most patients

- **Ongoing clinical trials of CAR-T cell therapy and others**

Tumor Agnostic Approval

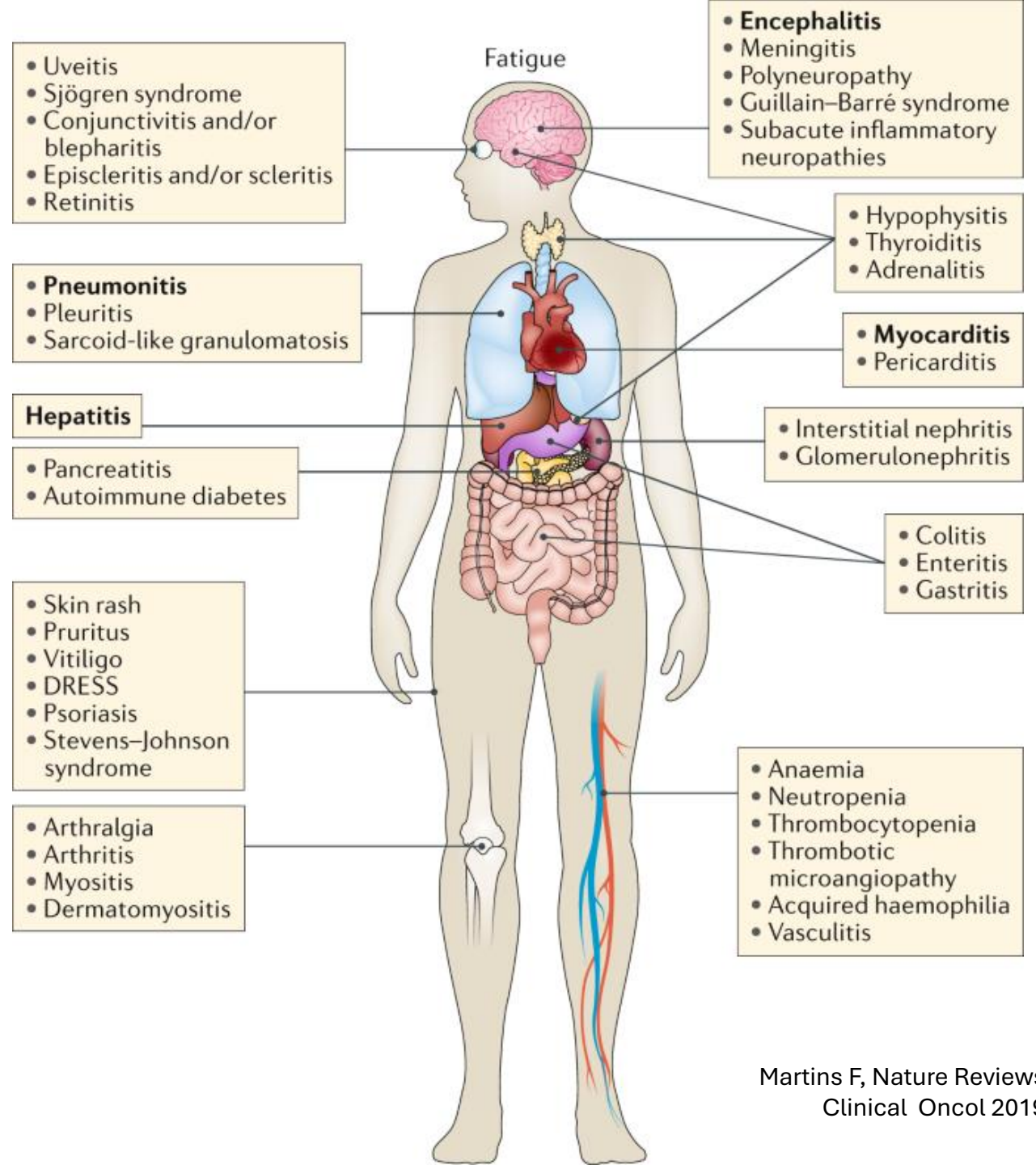
- **Unresectable or metastatic MSI-H/dMMR or TMB-H solid tumors that have progressed on standard therapy**
- **Pembrolizumab (approved 5/23/17)**
 - RR ~ 40%
 - DOR > 6 mo in 78% of patients
- **Dostarlimab (approved 8/17/21)**
 - RR ~ 41%
 - DOR 35 mo

Side Effects of Immune Checkpoint Inhibitors

Usually very well tolerated

Side effects relatively uncommon but can be dangerous

Management
Hold treatment
Consider steroids



Conclusions and Thank You!

- Immunotherapy uses immune system to fight cancer
- Role really depends on the cancer site and the biomarkers
- Biggest role in endometrial and cervical cancer patients
 - dMMR
 - PDL1 positive
- Side effects usually manageable but rare things can happen
- Clinical trials ongoing

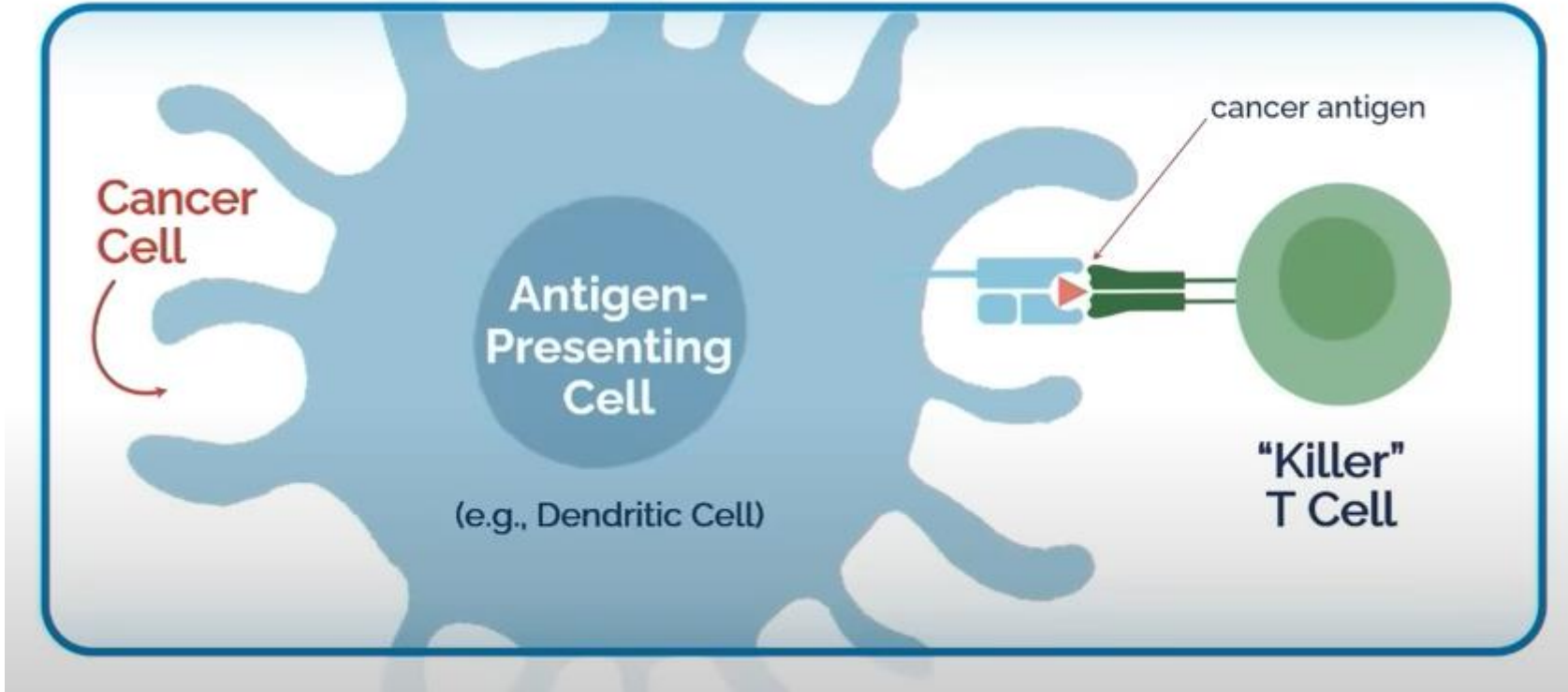


Innate

- Nonspecific
- Body's first line of defense against foreign substances and pathogens
- Skin
- Chemicals in blood
- Immune system cells

Adaptive

- More versatile
- Activated after innate
- Distinguishes self from non-self
- Protects against future reinfections
 1. Humoral immunity
 2. Cellular immunity

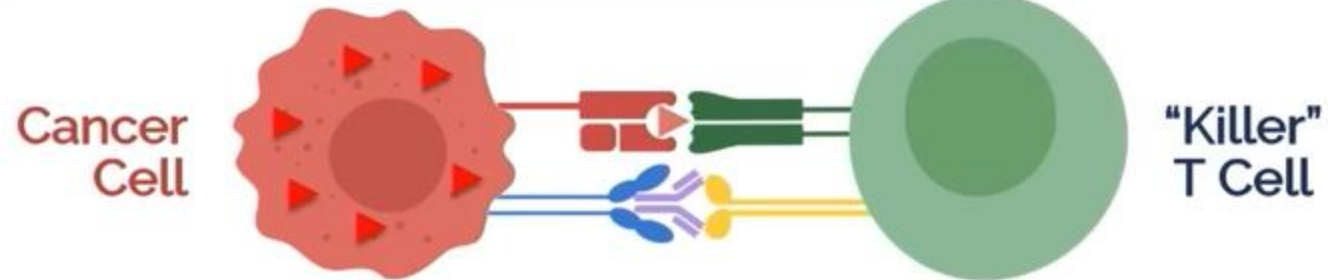


How Cancer Escapes the Immune System with Immune “Checkpoints”



Normally, PD-L1/PD-1 shuts down T cells

Can Checkpoint Immunotherapy Promote Anti-Cancer Activity?

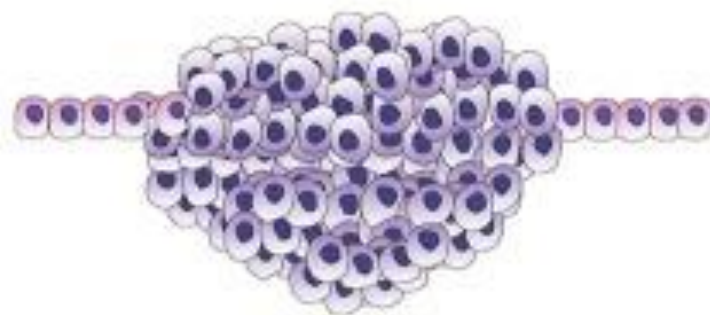


PD-L1/PD-1 Pathway Blocked!

Tumor Initiation

In situ Carcinoma

Metastatic Dissemination



*Natural killer cells.
CD8+ T cells.
Th1 CD4+ T cells.
Cytotoxic macrophages
and neutrophils.*

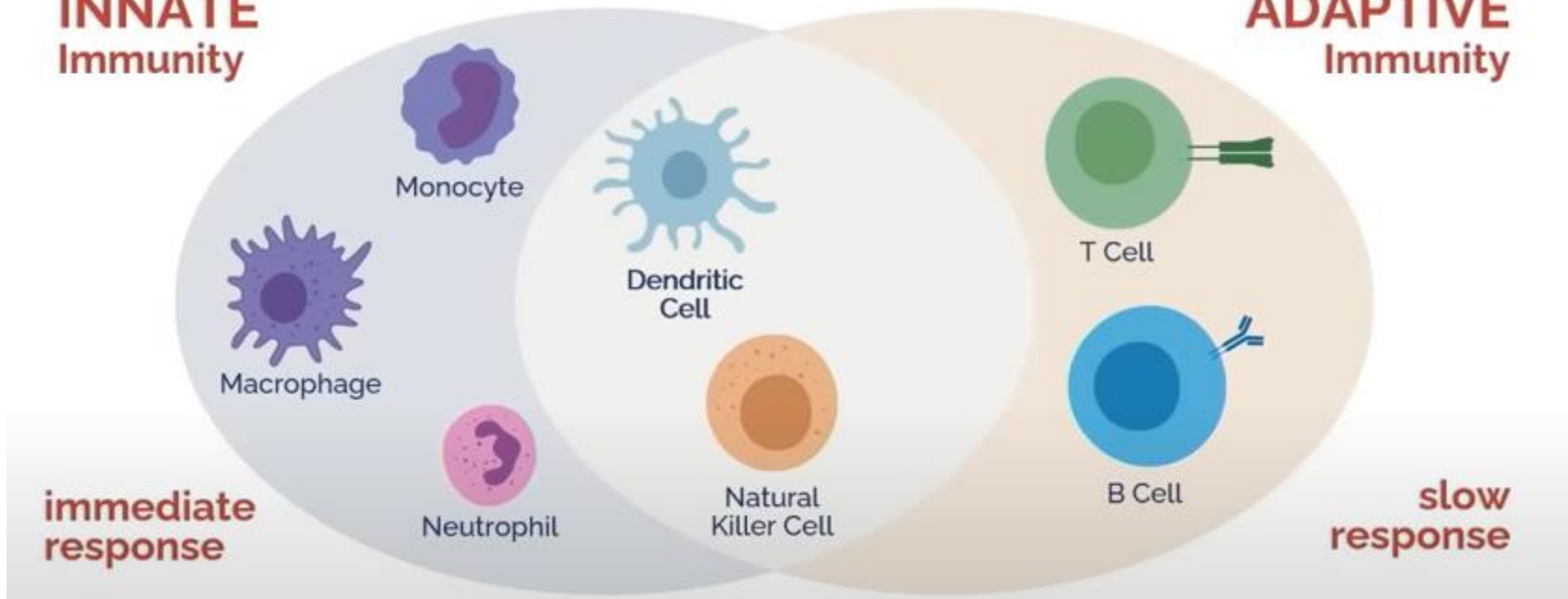
Tumoricidal effector response

Immune Tolerance

*Pro-tumoral macrophages.
Regulatory T cells.
Regulatory B cells.
Immature DCs.
Pro-metastatic neutrophils.*

INNATE
Immunity

ADAPTIVE
Immunity



immediate
response

slow
response

Brief Review of immune system

INNATE

- Physical barriers
- Chemical components
- NK cells – lymphocytes that recognize altered or stressed tissues, MHC I
- Macrophages – inflammation, cytokines, chemokines, angiogenesis, up and down regulate immunity
- Dendritic cells – antigen presenting cells

ADAPTIVE

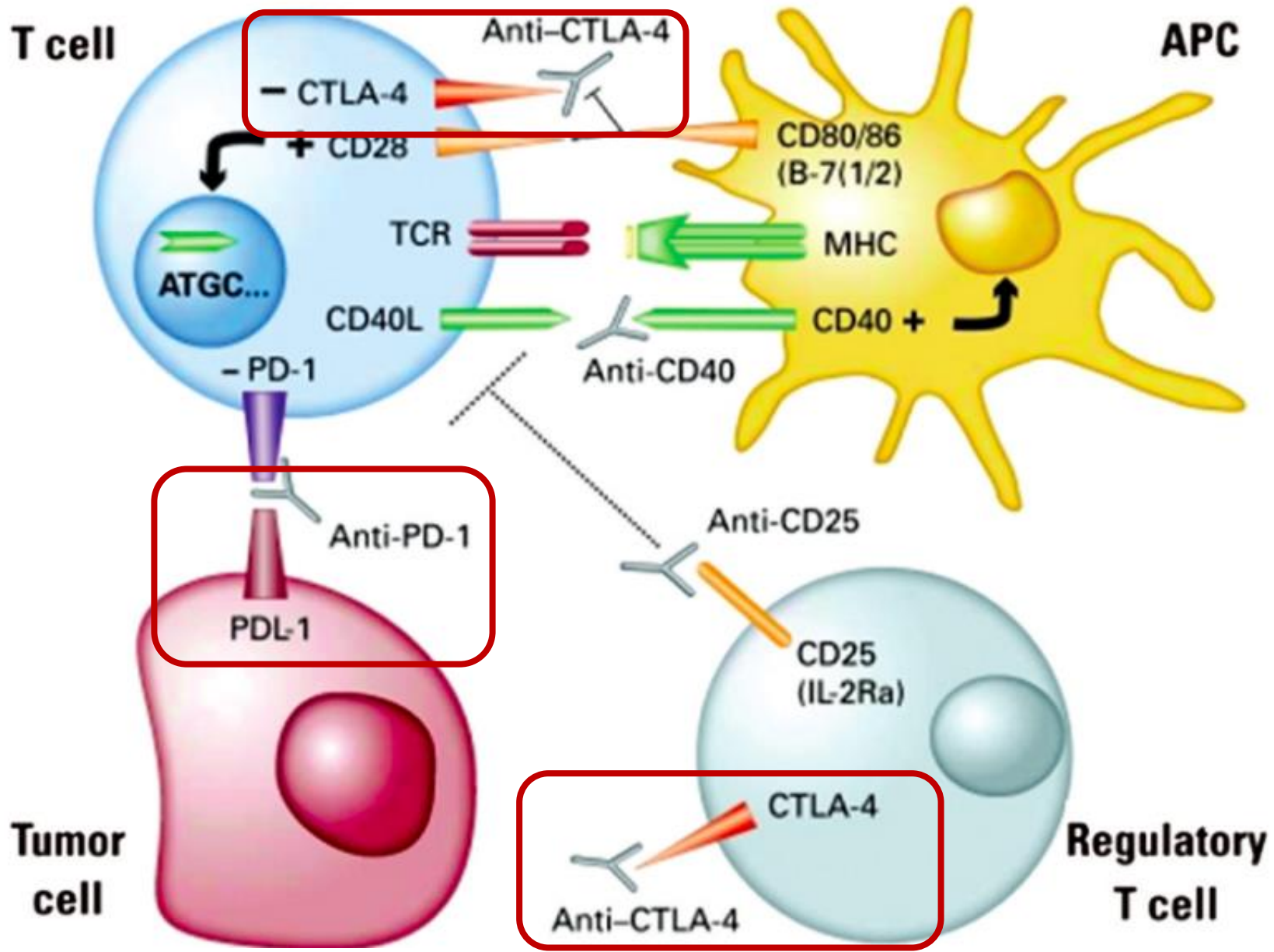
- T lymphocytes – response to antigens presented on MHC (HLAs)
 - CD4 – MHCII
 - CD8 - MHC I
- B lymphocytes – humoral immunity, antibodies

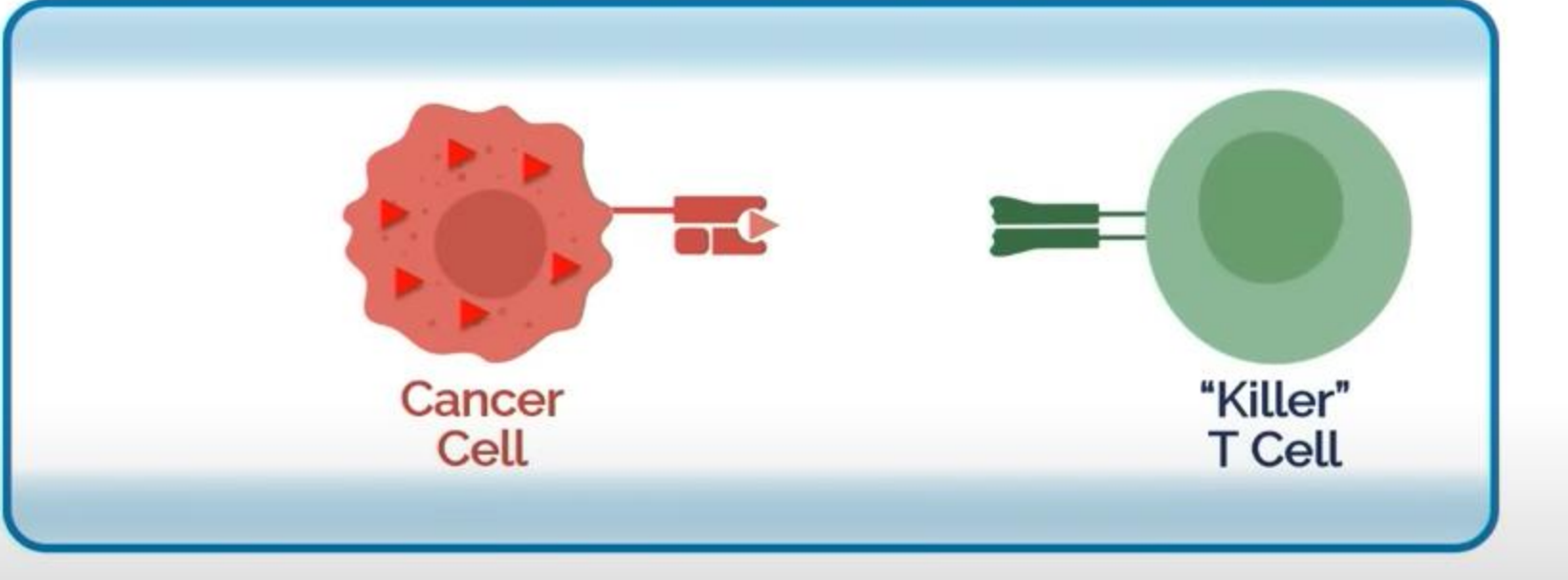
Immune system and Cancer

- Immune system plays a significant and complex role to prevent tumor initiation, progression, and metastases
- Cancer can outsmart the immune system in several ways
- Downregulate antigen presentation
- Decrease MHC-I complex expression -> prevent T lymphocyte activation
- Tumors can secrete proteins that inhibit T-cell effector action
- Promote Treg development -> suppress immune function
- Downregulate intracellular adhesion molecules
- Change molecules responsible for apoptosis
- Development of peripheral tolerance

- Initiate distinction between self and nonself
- CD8+ lymphocytes (cytotoxic T cells)
- CD4+ lymphocytes (helper T cells)
- Natural killer cells (NK cells)

Immunotherapy

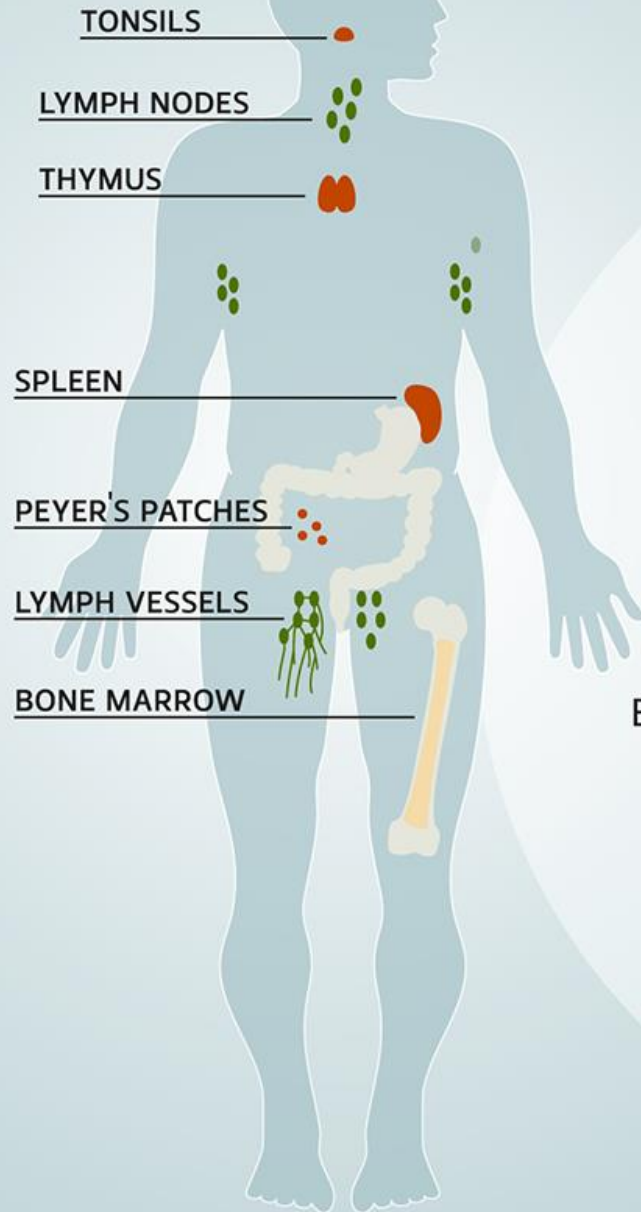




Types of Immunotherapy

- Checkpoint inhibitors (PD1, PDL1, CTL4) – allow immune system to recognize and attack cancer
- Chimeric antigen receptor (CAR)T-cell therapy – takes T cells from a patients blood, mixes with virus, gives back
- Cancer vaccines – given to start immune response
- Monoclonal antibodies - designed to attack
- Oncolytic viruses – modified viruses

Components of the Immune System



WHITE BLOOD CELLS (WBCs)

- The cells of the immune system
- Made inside bone marrow
- WBCs travel through the body inside lymph vessels, which are in close contact with the bloodstream

THERE ARE SEVERAL TYPES OF WBCs



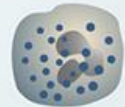
NEUTROPHILS
Engulf & destroy



**MONOCYTES
(MACROPHAGES)**
Engulf & destroy



EOSINOPHILS
Fight parasitic
infections



BASOPHILS
Release
histamine



LYMPHOCYTES
Attack specific
pathogens



PLASMA CELLS
Produce
antibodies