ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanisms of Immune-Related Adverse Events

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AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

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Society for Immunotherapy of Cancer

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Disclosures

- Consultant: Amgen, Roche, Nektar
- I will be discussing non-FDA approved indications during my presentation.

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Immune Related Adverse Events
Mechanisms, Management, Mitigation

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Outline

- Basic principles of immunological tolerance and autoimmunity
- Differential roles of CTLA-4 and PD-1 in maintenance of tolerance
- Mechanisms of breakdown of tolerance by checkpoint blockade

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FDA- Approved Immune Checkpoint Blockers

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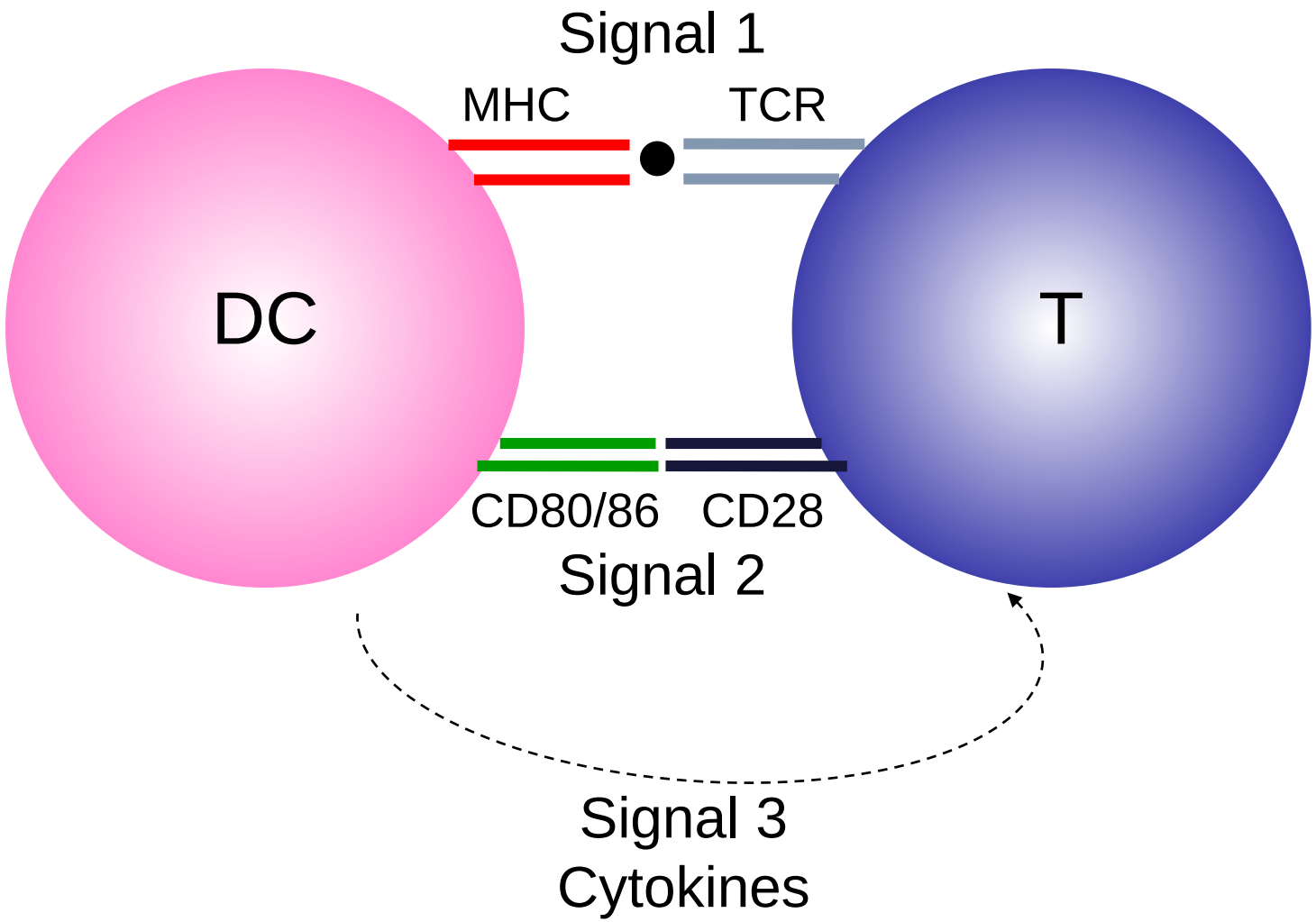
Postow et al NEJM 2018

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

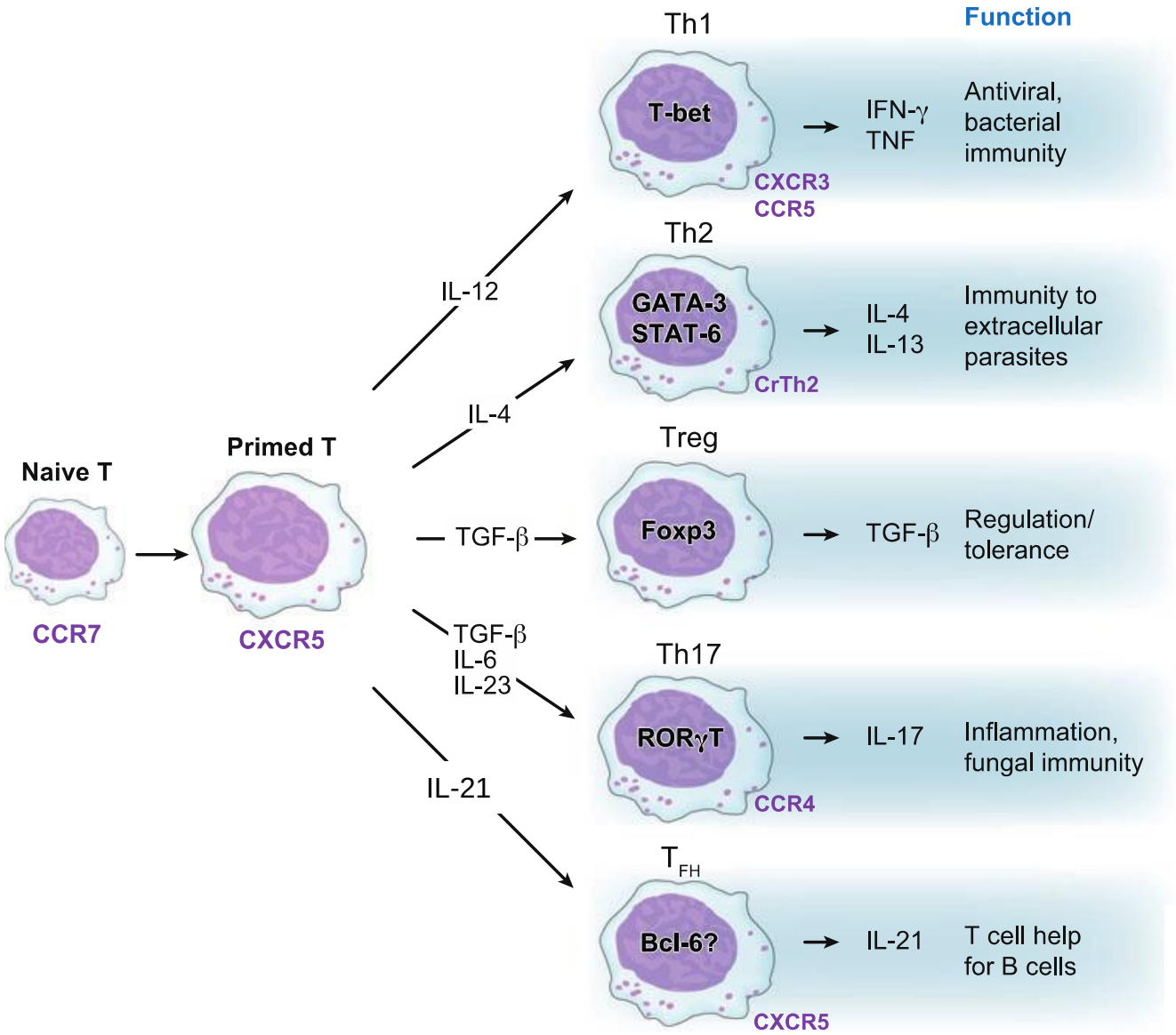
Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

For full T cell activation and differentiation, T cells need 3 signals



Depending on cytokines from DCs, naïve CD4 T cells differentiate into effector subsets



Oncologists
Virologists

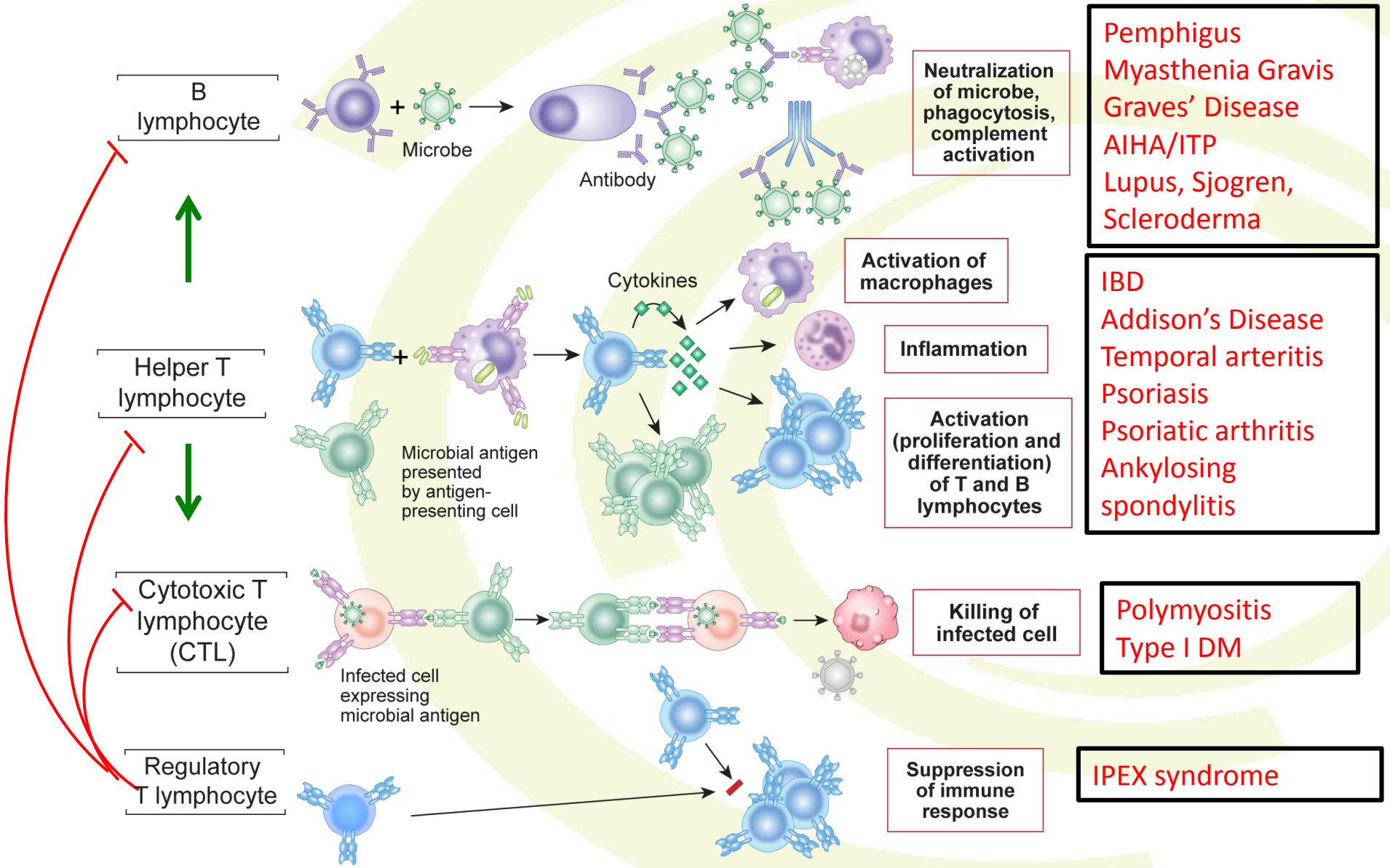
Allergy specialists
Pulmonologists

Everyone

Rheumatologists

Rheumatologists

Major Effector Cells of the Immune System



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Most Autoimmune Diseases are due to Failure of T cell Tolerance

Immunologic Tolerance:
unresponsiveness of immune system to self antigens

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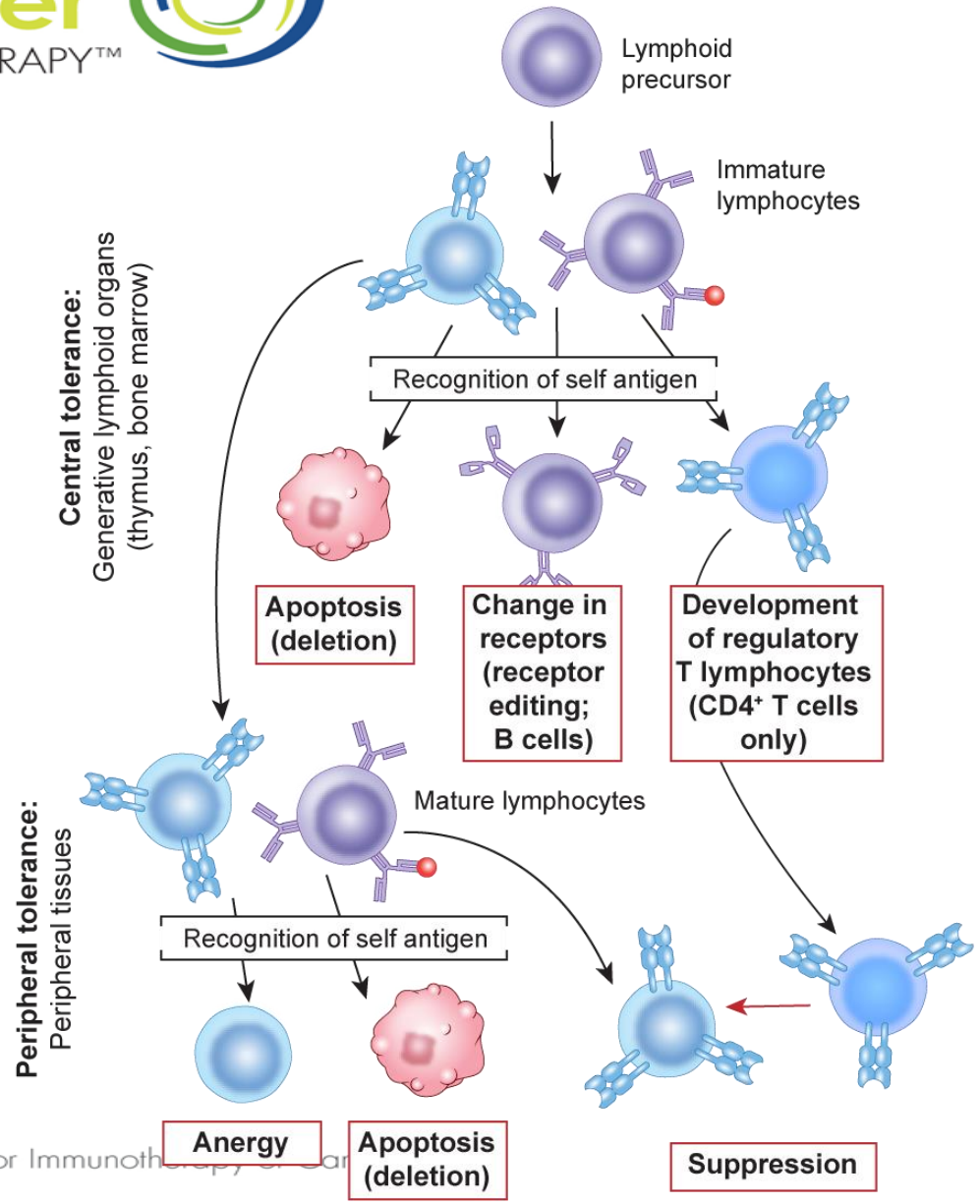
Central and Peripheral Tolerance



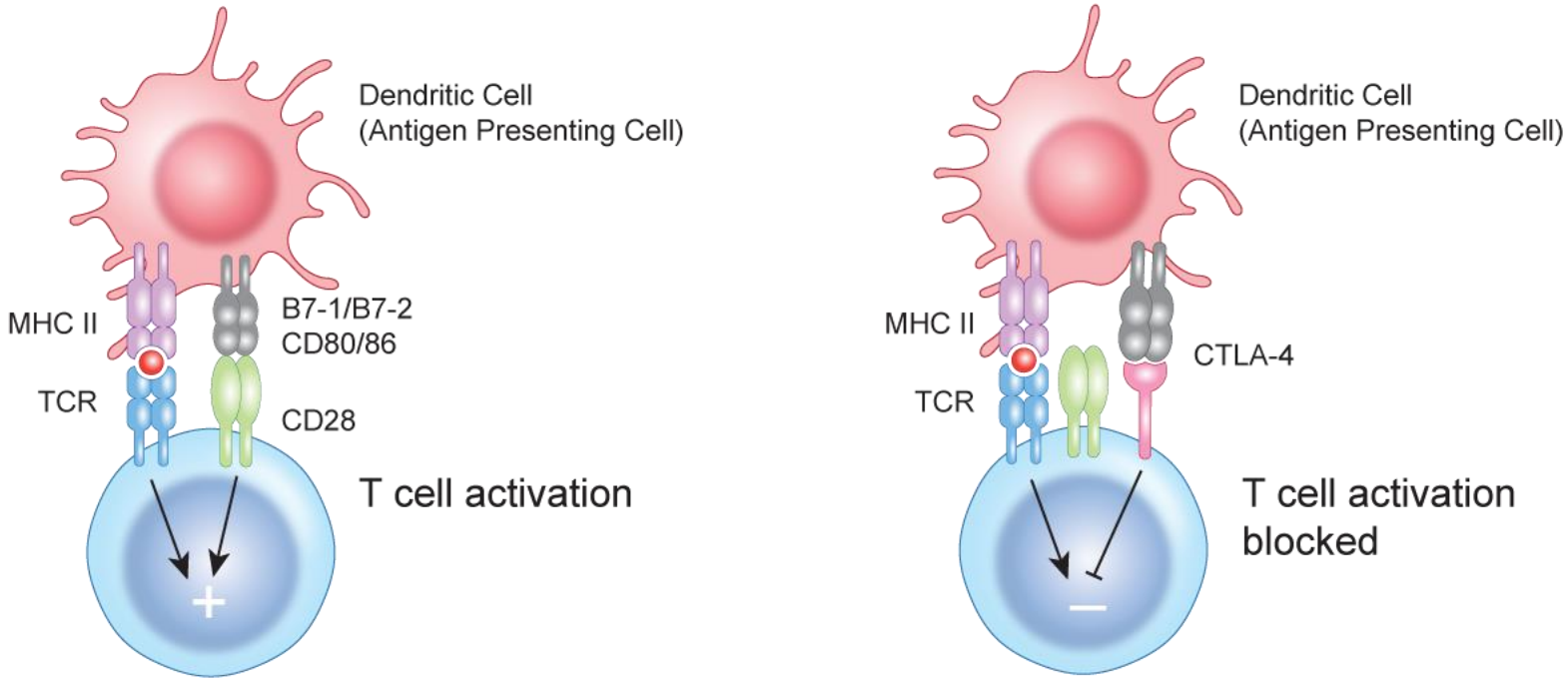
Central Tolerance

- For T cells it occurs in the thymus
- Fate of high affinity, self-reactive T cells is death (deletion) and removal from T cell pool
- Some survive as regulatory (suppressor) T cells while others escape to peripheral tissues

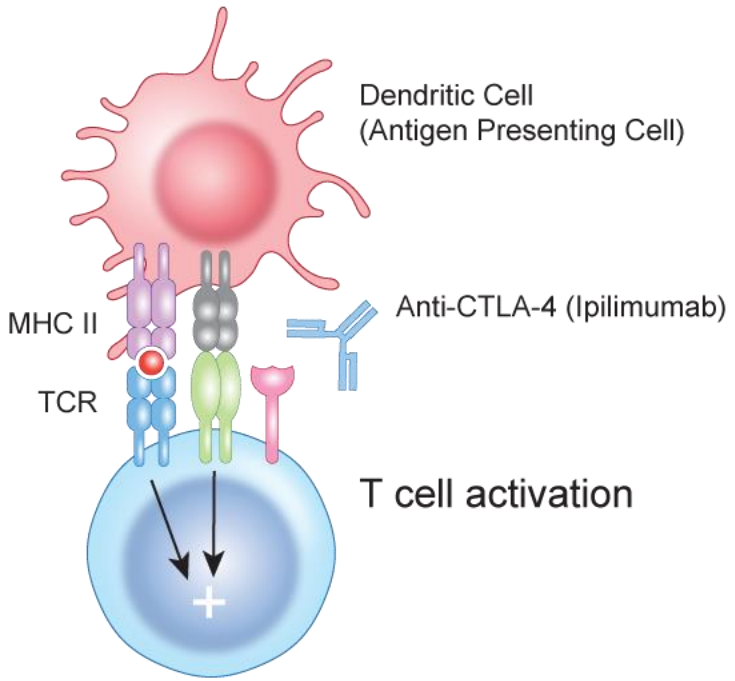
Peripheral Tolerance

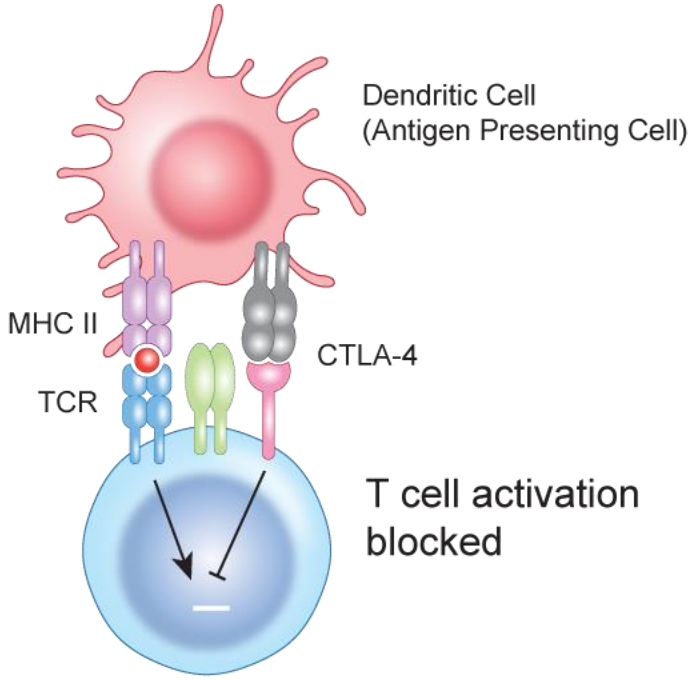
- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (ane

CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules



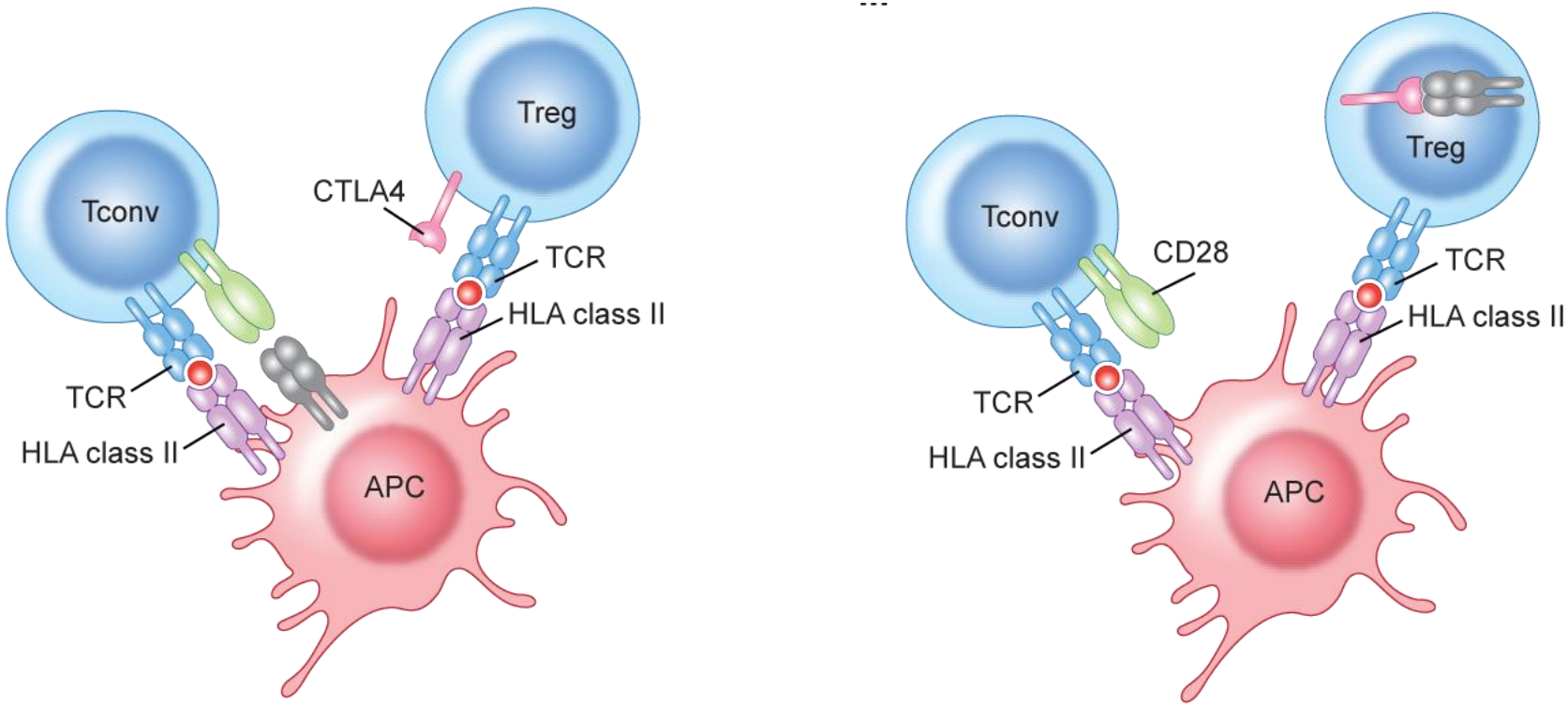
Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation





Breakdown of peripheral tolerance leading to activation of self-reactive T cells

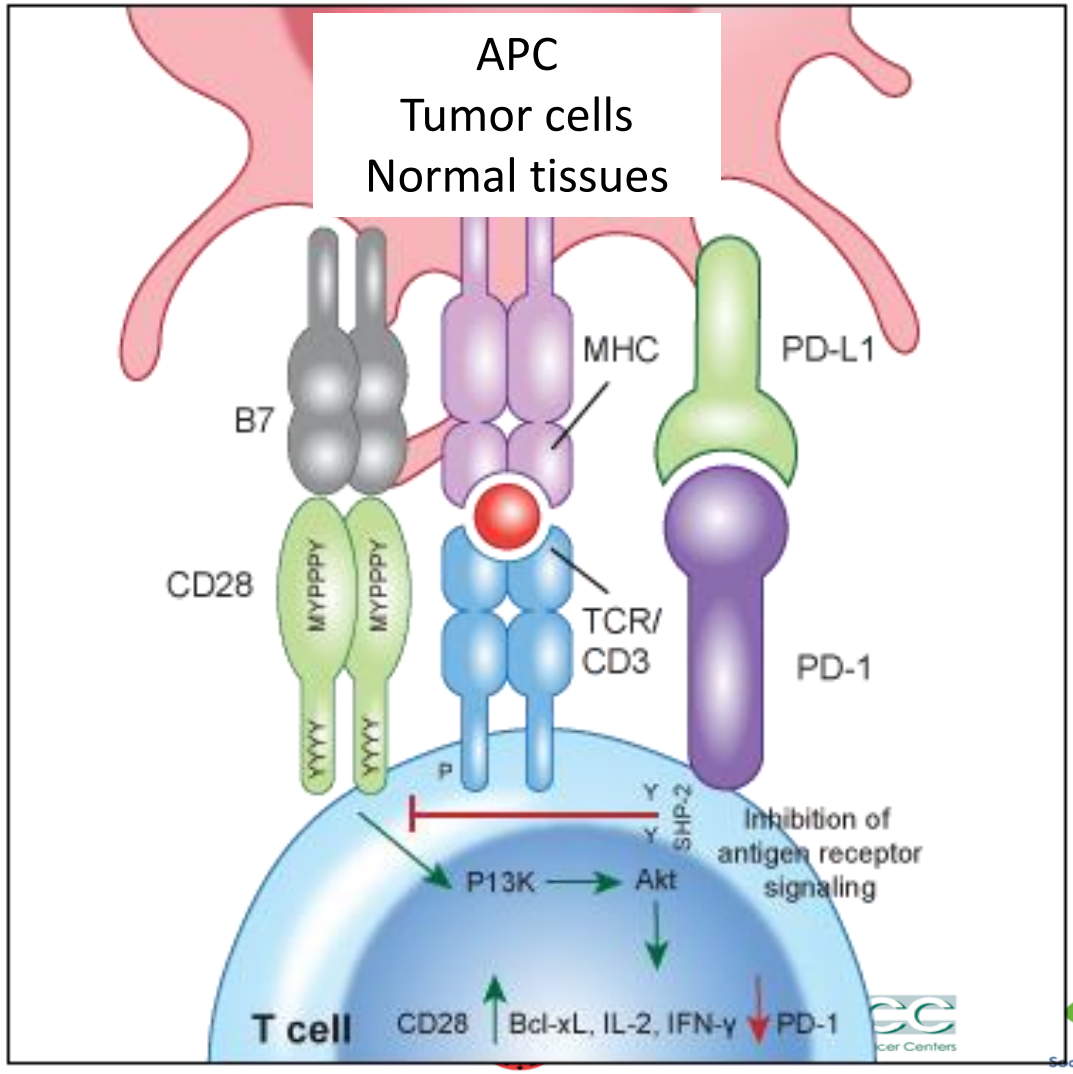
Regulatory T cells (Tregs) use CTLA-4 to remove B7 molecules from surface of antigen presenting cells to prevent activation of self reactive T cells



Anti-CTLA-4 (ipilimumab) may interfere with inhibitory function of Tregs

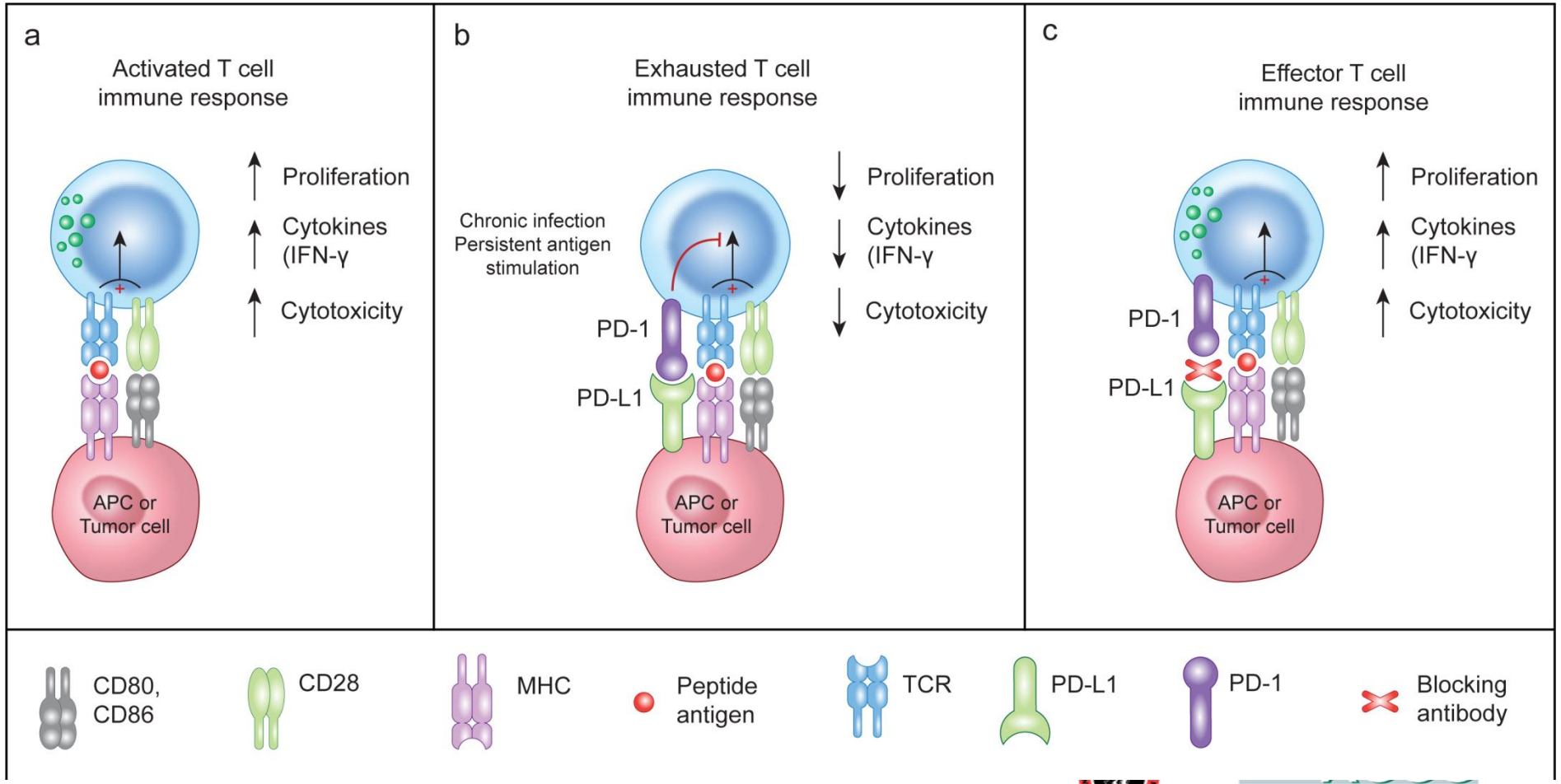
Interaction of PD-1 with its ligands, PD-L1/PD-L2 inhibits CD28 signaling in T cells

- PD-1 is upregulated on T cells after activation
- PD-L1 is found on both immune and non-immune cells in peripheral tissues
- PD-L2 is mostly found on immune cells in response to inflammatory stimuli
- In contrast, CTLA-4 and its ligands are only found on immune cells
- Mice deficient in PD-1 have delayed development of autoimmune disease compared to CTLA-4 deficient ones



Blocking PD-1/PD-L1 Pathway Reactivates T cells

PD-1 is the receptor on T cells – its ligand PD-L1 is on immune cells or tumor cells



IRAE MECHANISM

- Development of autoimmunity:
  - Release of Auto-reactive T cells
  - Generation of pre-existing Auto-reactive Antibodies
  - On target attack of shared tumor antigens on normal tissue
- Target tissue expression of Immune Checkpoint (e.g. CTLA4 on normal Pituitary)
- Inflammatory Cytokine release (e.g. IL-17 and colitis)

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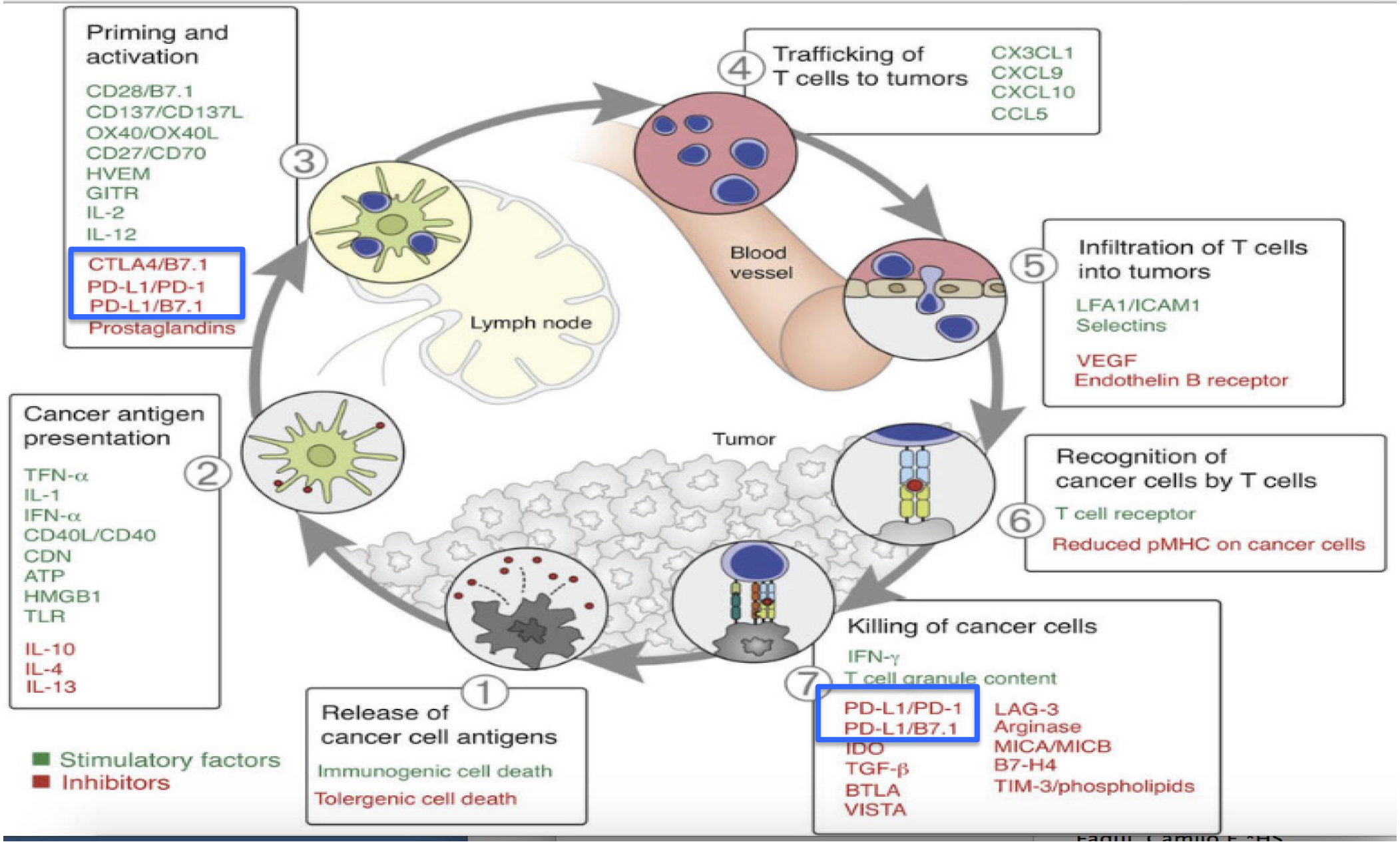
IRAE MECHANISM: Immune Cycle
Locations of Immune Checkpoint Control

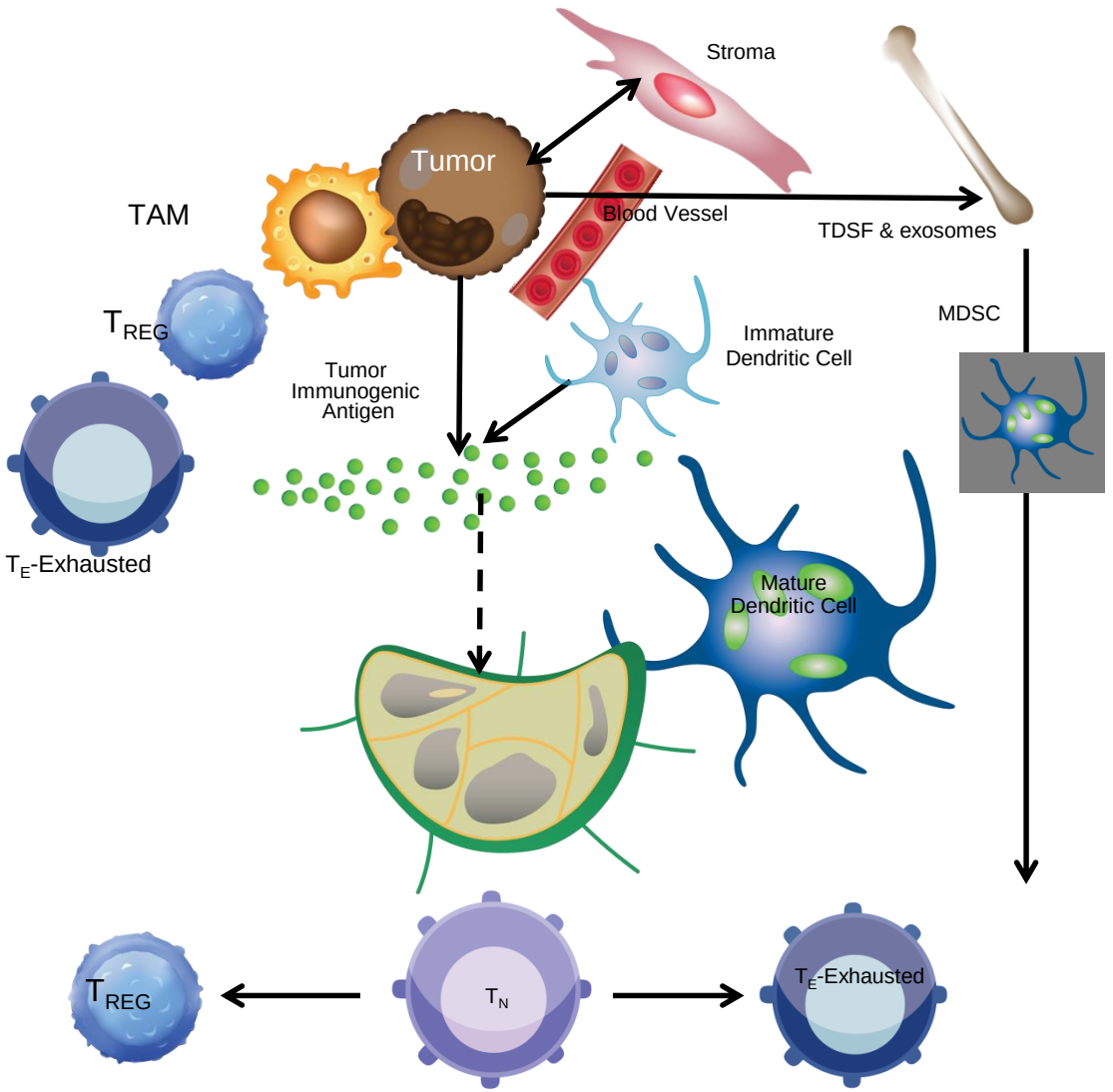
From Chen & Mellman Immunity 2013



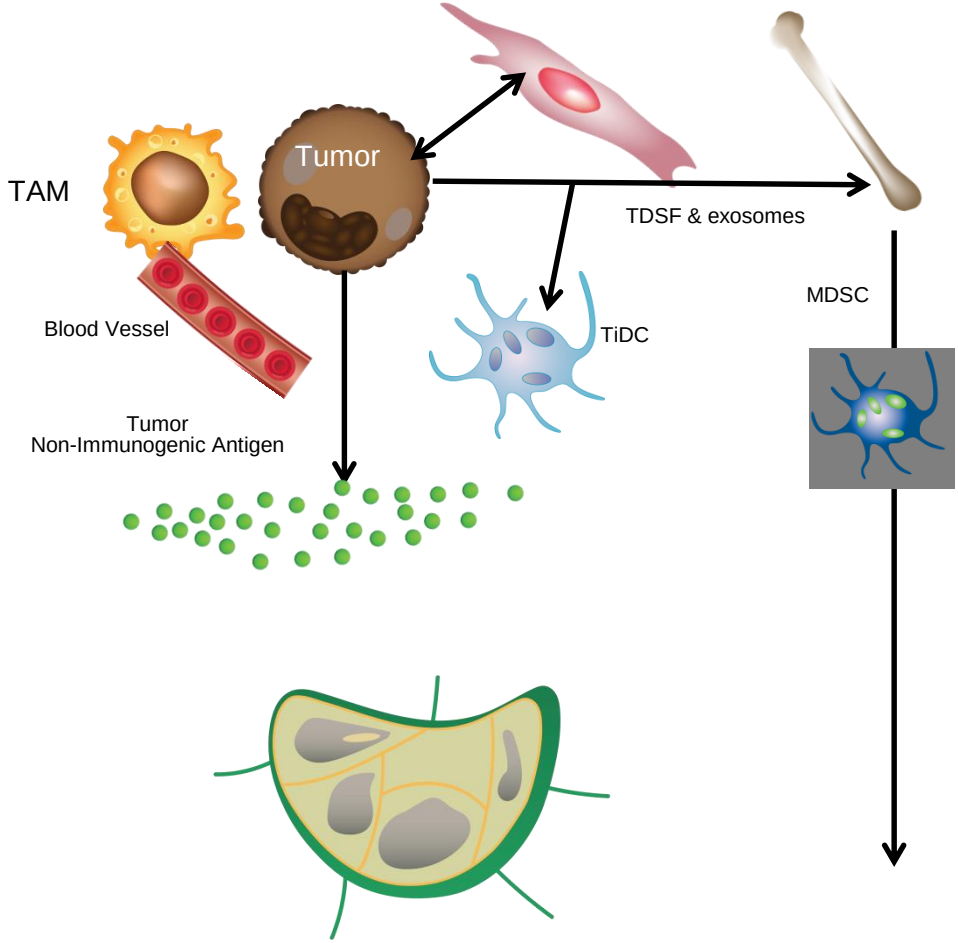
IRAE MECHANISM: 3 E's of Immunology: Escape
PD1 and CTLA4 Axes Role in Tumor Escape

Adopted from
Dunn, Old & Schreiber
Annual Review of Immunol
2004

IMMUNOGENIC TUMOR



NON-IMMUNOGENIC TUMOR



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IRAE MECHANISM

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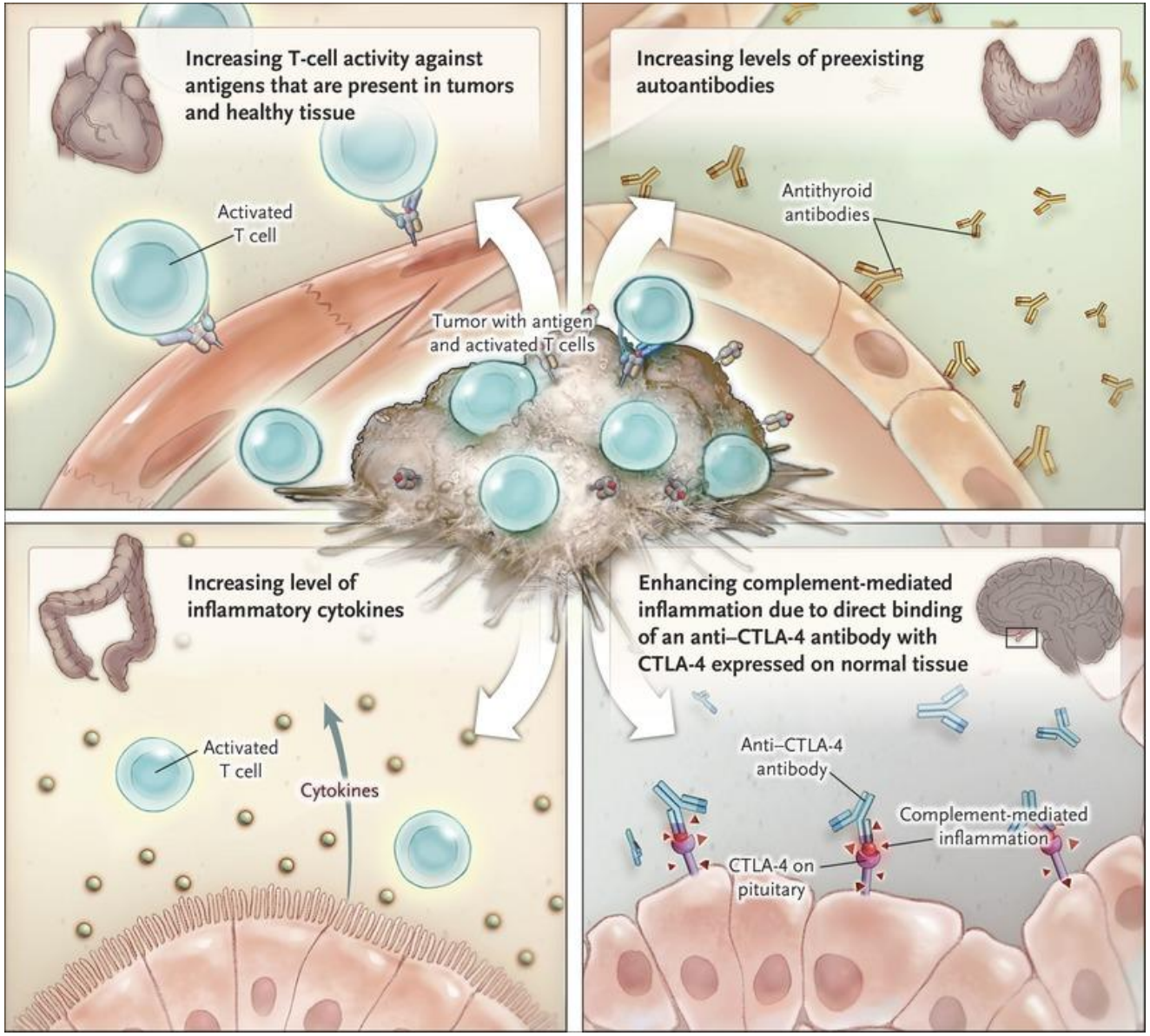

Early and late irAEs may occur by distinct mechanisms

Early and common

Mucosal

Colitis

Dermatitis

Pneumonitis

Global Regulatory T cell dysfunction

↓

Activation of Effector T cells (Th_{17})

↓

Recruitment of inflammatory cells (neutrophils)

Late and rare

Specific organ

Hypophysitis (other endocrine)

Myocarditis; Neurologic

Arthritis; Vitiligo

Breakdown of organ specific tolerance

↓

- Activation of tumor specific T cells that recognize antigen shared between tumor and healthy tissue: vitiligo, myocarditis
- Activation of tissue specific anergic T cells that recognize antigen distinct from the tumor
- Activation of autoreactive Tfh cells and B cells with resultant production of autoantibodies

↓

T cell or antibody mediated tissue destruction

Summary

- CTLA-4 expression on effector and regulatory T cells prevents co-stimulation through CD28 and maintains T cell anergy and peripheral tolerance
- Activation of PD-1 on activated T cells by its ligands renders them non-functional
- CTLA-4 and PD-1 are important in maintenance of peripheral immune tolerance
- The irAEs can be divided into two general categories of “early and common” vs. “late and rare”. Th17 cells might play a role in early and common type irAEs while B cells and/or CD8 T cells might play a role in late and rare type irAEs