ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanisms of Immune-Related Adverse Events

Michael Morse, MD

Duke University Health System

AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

sitc
Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Disclosures

- Consulting Fees and honoraria
  - BMS, Merck, Genentech, Merck KGA
- Research Support
  - Astrazeneca/Medimmune
- I will not be discussing non-FDA approved indications during my presentation.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immune-related Adverse events (irAE): The players

Inferences from Autoimmune Disease

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

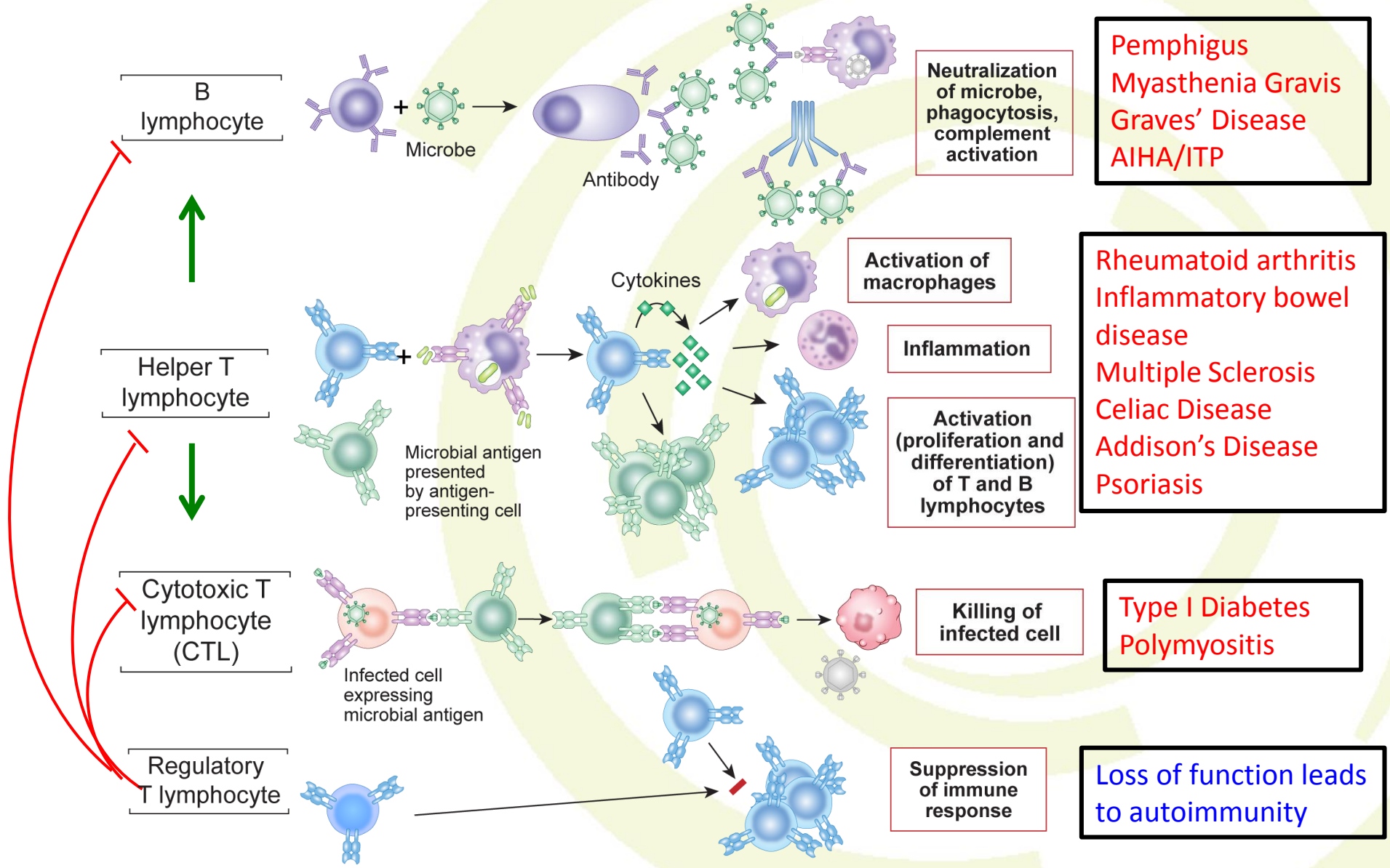
Most Autoimmune Diseases are due to Failure of T cell Tolerance (even in those diseases that are antibody-mediated)

Immunologic Tolerance: unresponsiveness of immune system to self antigens

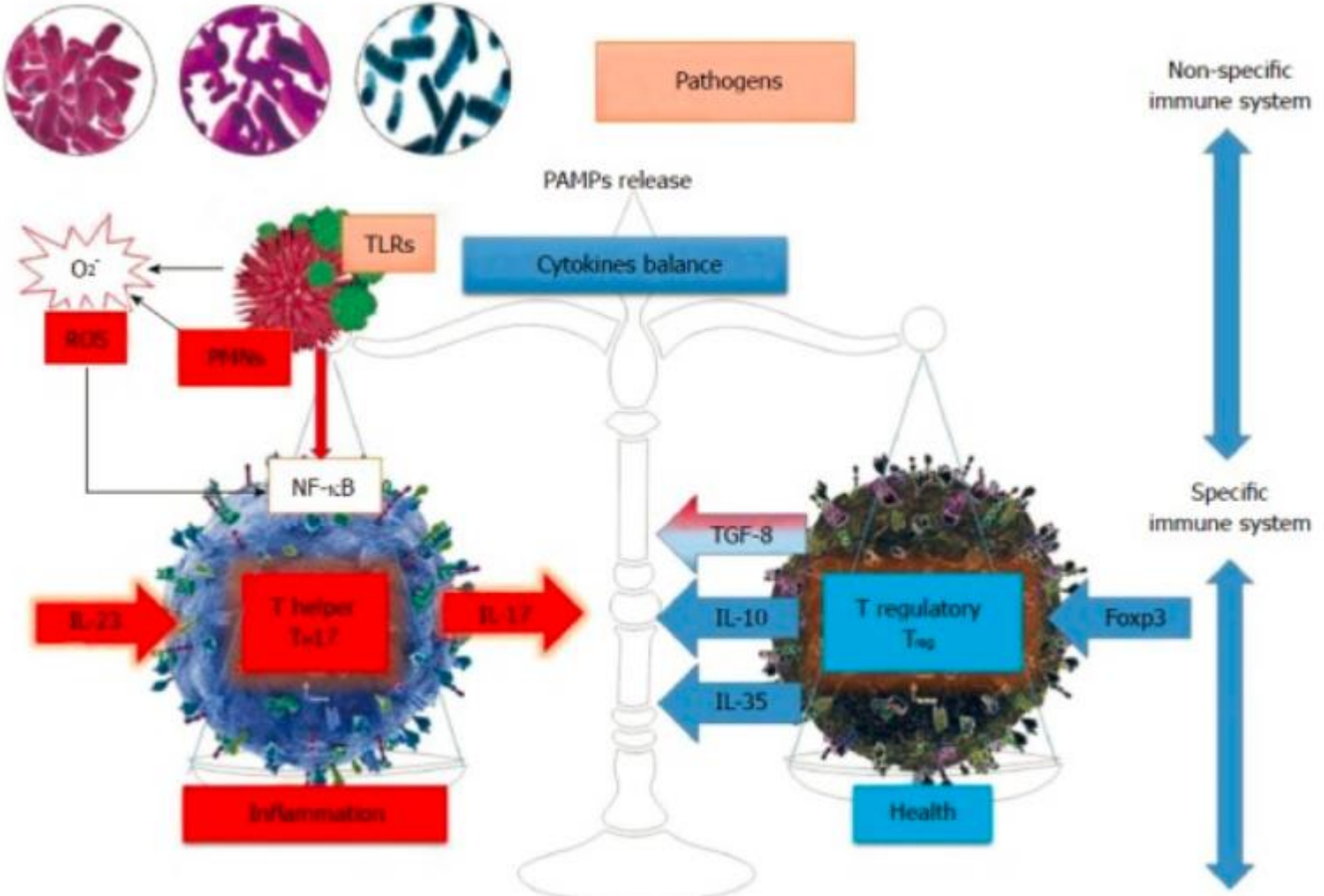
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Major Effector Cells of the Immune System



Immunological Balance in inflammatory bowel dz



World J Gastroenterol. 2015 May 21; 21(19): 5823–5830

ADVANCES IN Cancer IMMUNOTHERAPY™

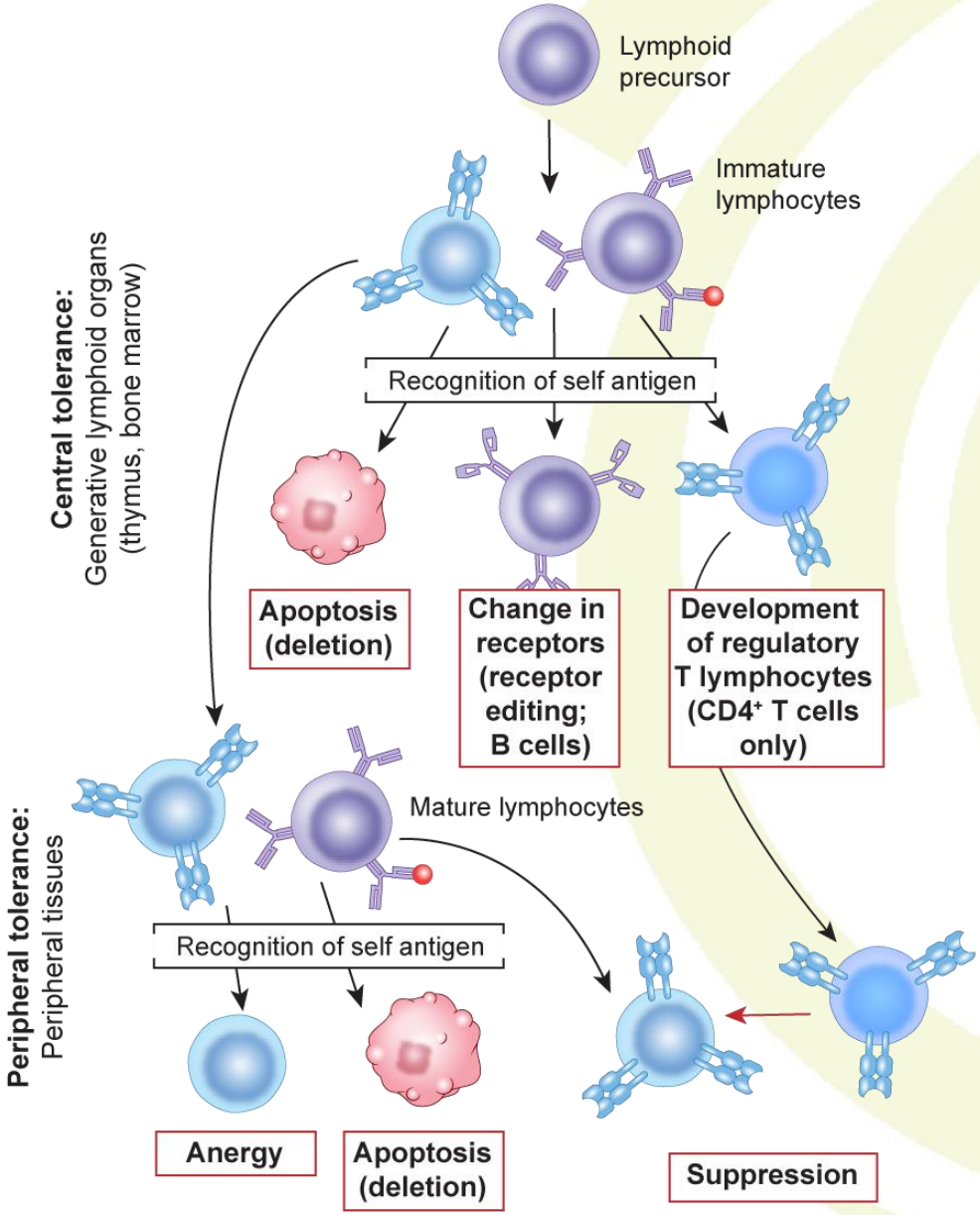
Immune-related Adverse events (irAE):

Inferences from basic biology

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Central and Peripheral Tolerance



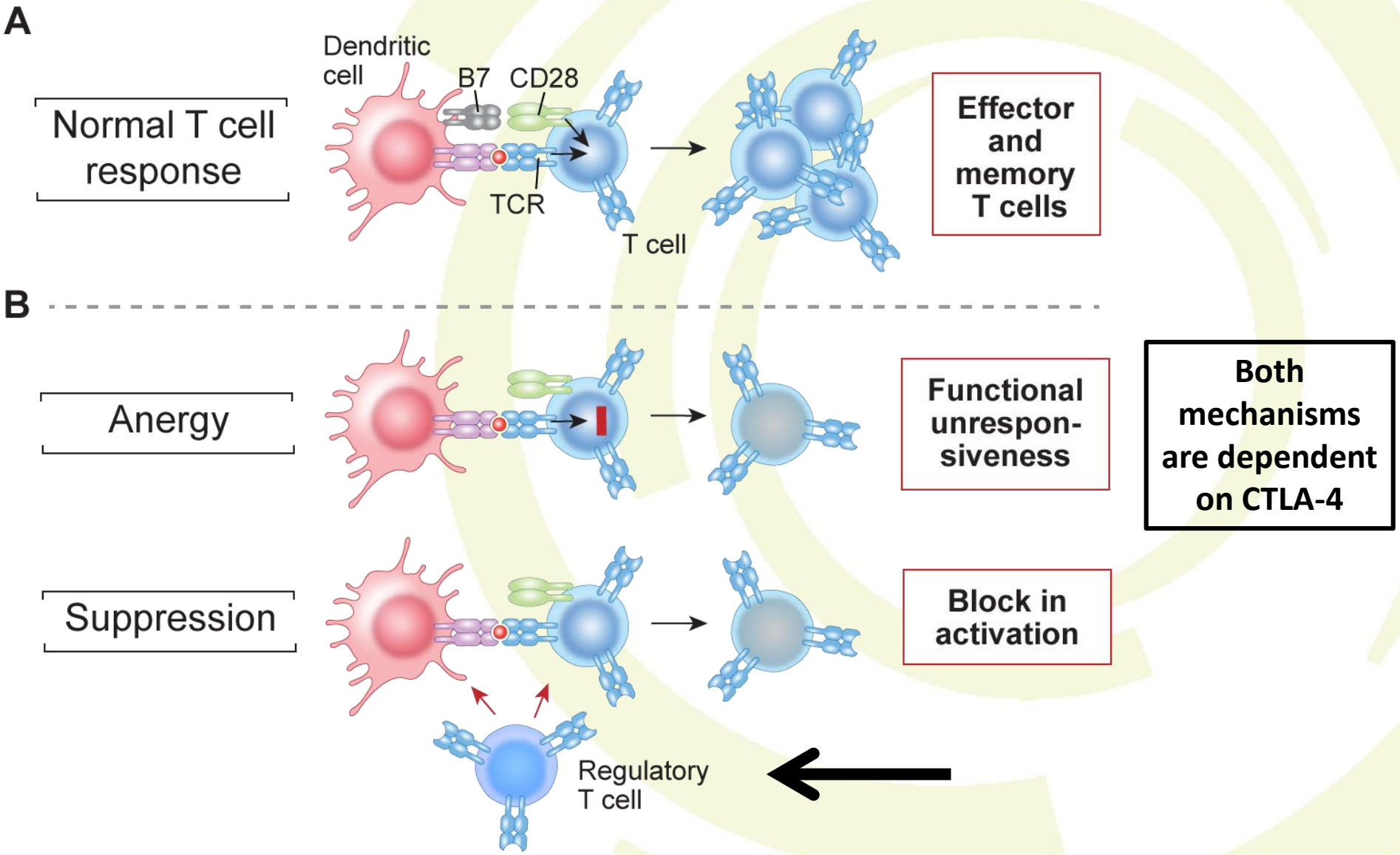
Central Tolerance

- 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

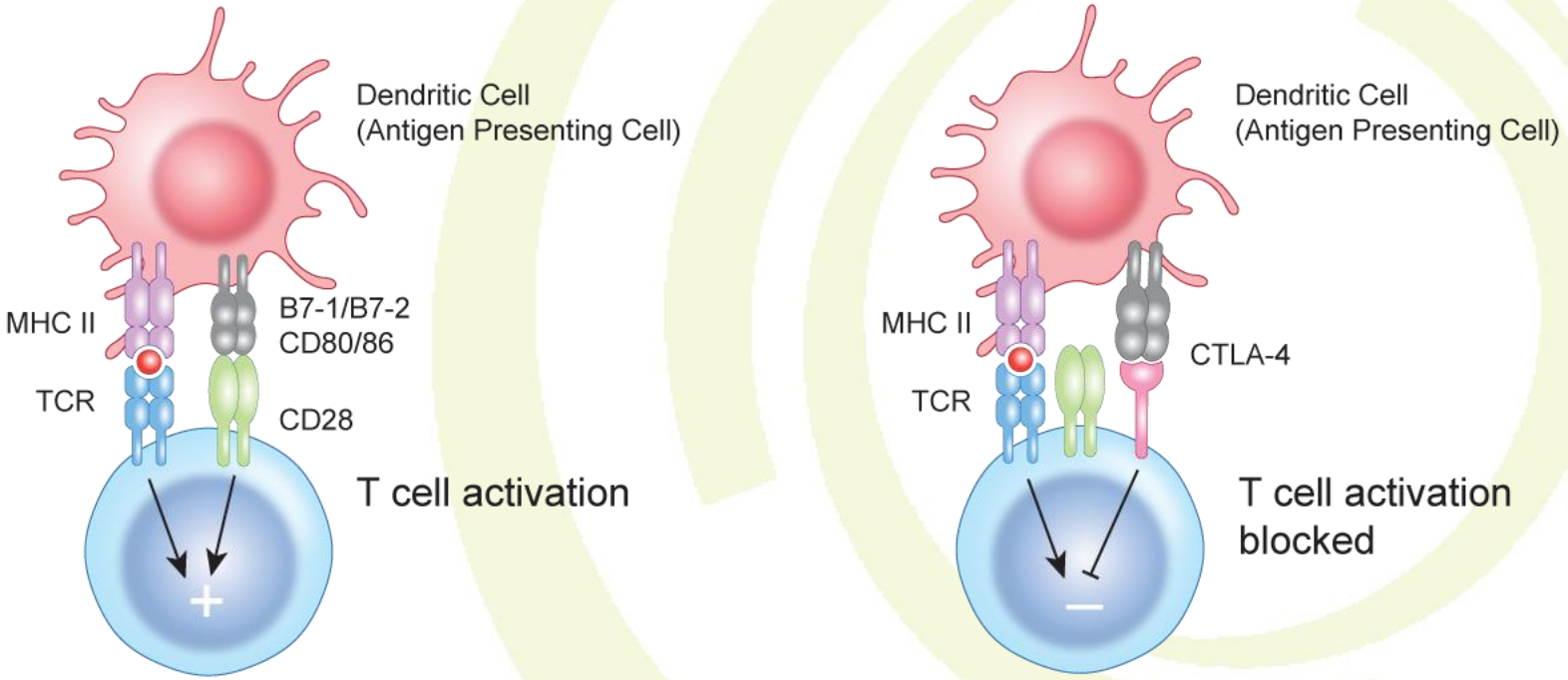
Peripheral Tolerance

- 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 (anergic)

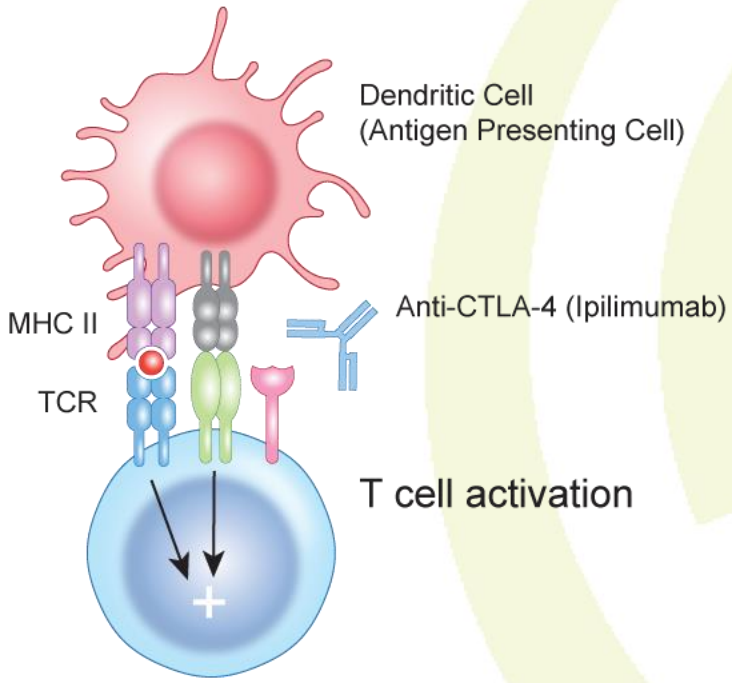
Peripheral tolerance occurs in the absence of CD28 dependent co-stimulation

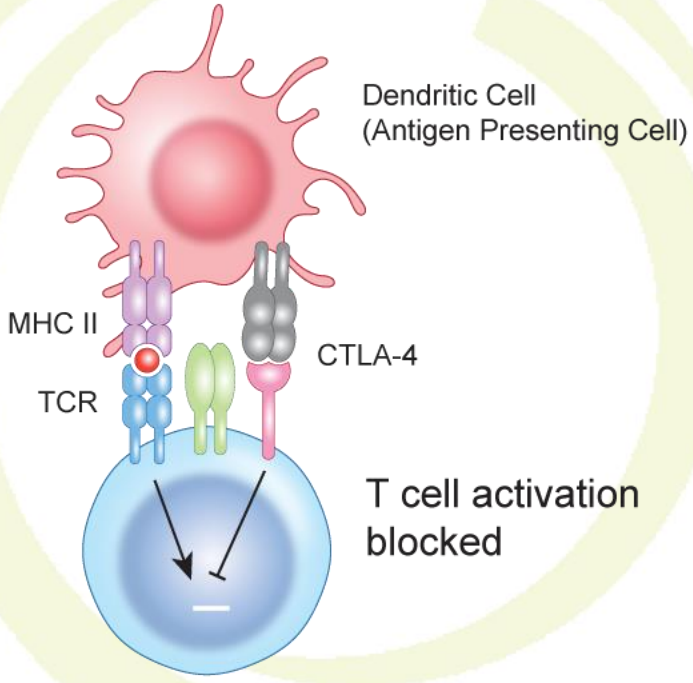


CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules



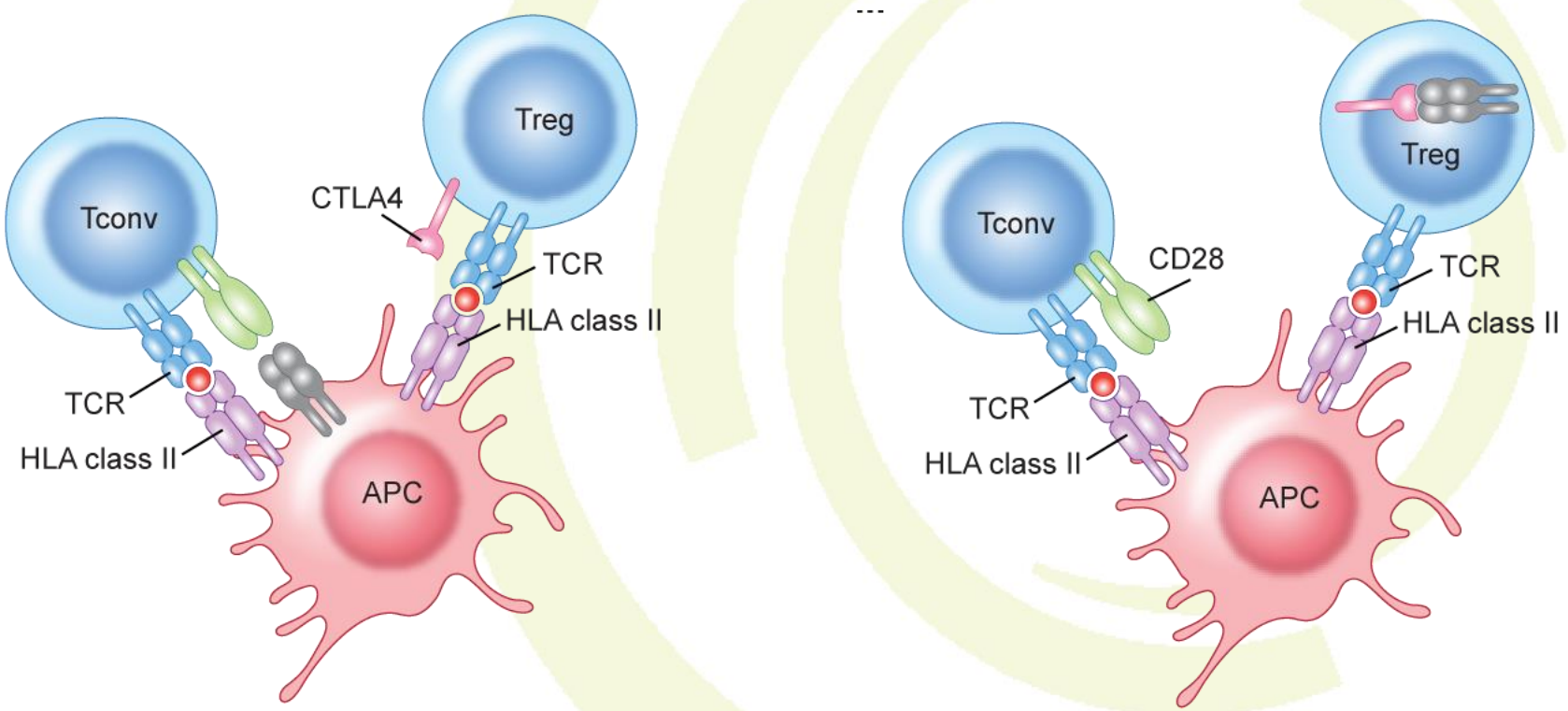
Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation





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

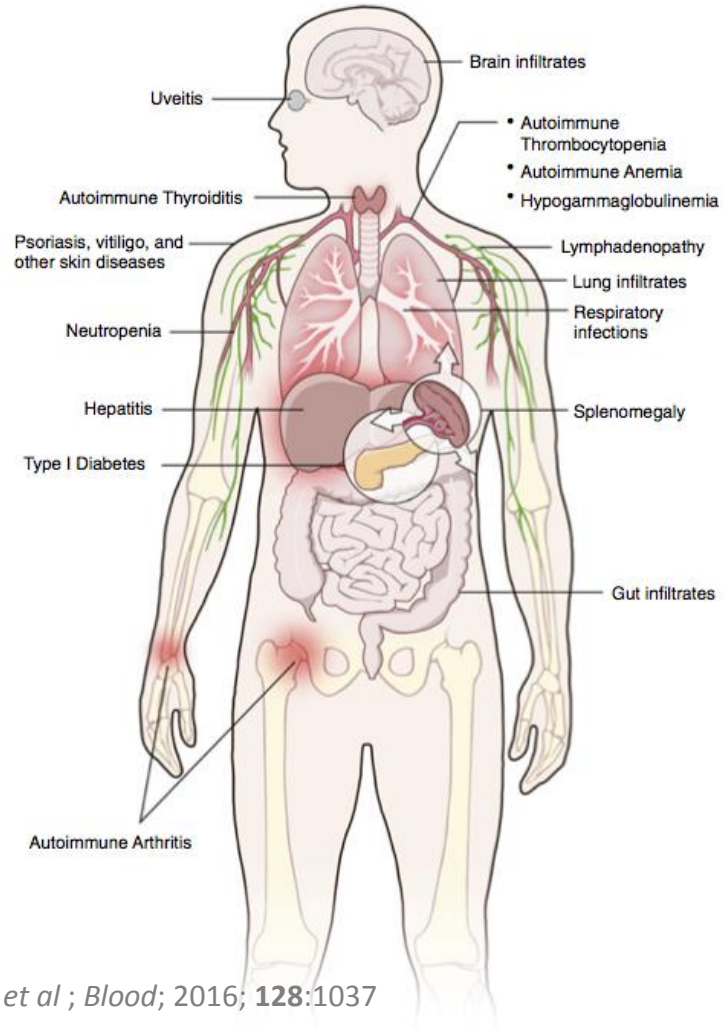
Regulatory T cells (Tregs) use CTLA-4 to remove B7 molecules from surface of antigen presenting cells to prevent activation of self reactive T cells



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

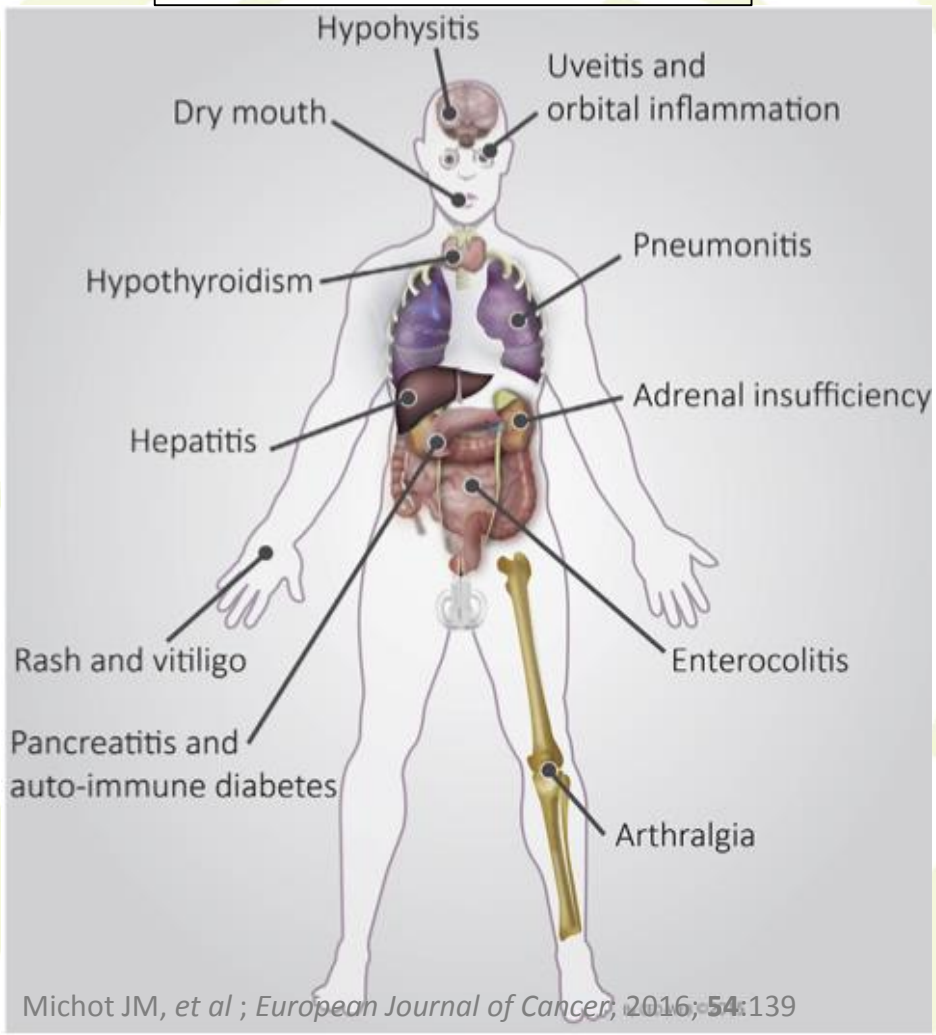
People with CTLA-4 haploinsufficiency develop a spectrum of autoimmune diseases similar to the irAEs observed with ipilimumab

CHAI/LATAIE Phenotype



Lo, B. *et al* ; *Blood*; 2016; **128**:1037

Ipilimumab irAEs



Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

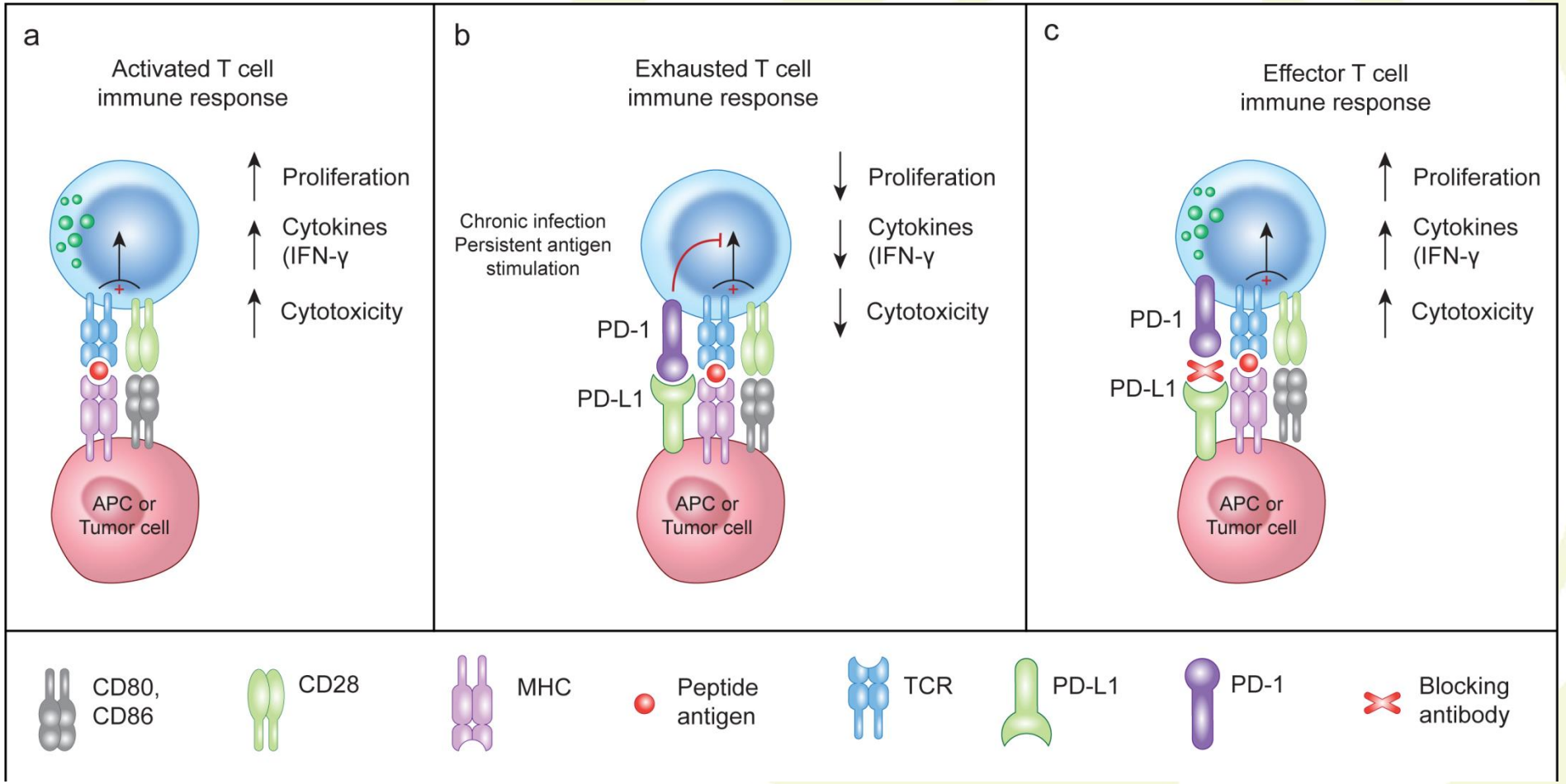
Polymorphisms in CTLA-4 gene has been linked to human autoimmune diseases

Autoimmune Disease	Polymorphism
Thyroiditis, Graves' disease, Hashimoto's disease	CTLA-4
Diabetes mellitus	CTLA-4
Celiac disease	CTLA-4
Myasthenia gravis	CTLA-4
Lupus	CTLA-4
Rheumatoid Arthritis	CTLA-4
Addison's disease	CTLA-4

Adapted from Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

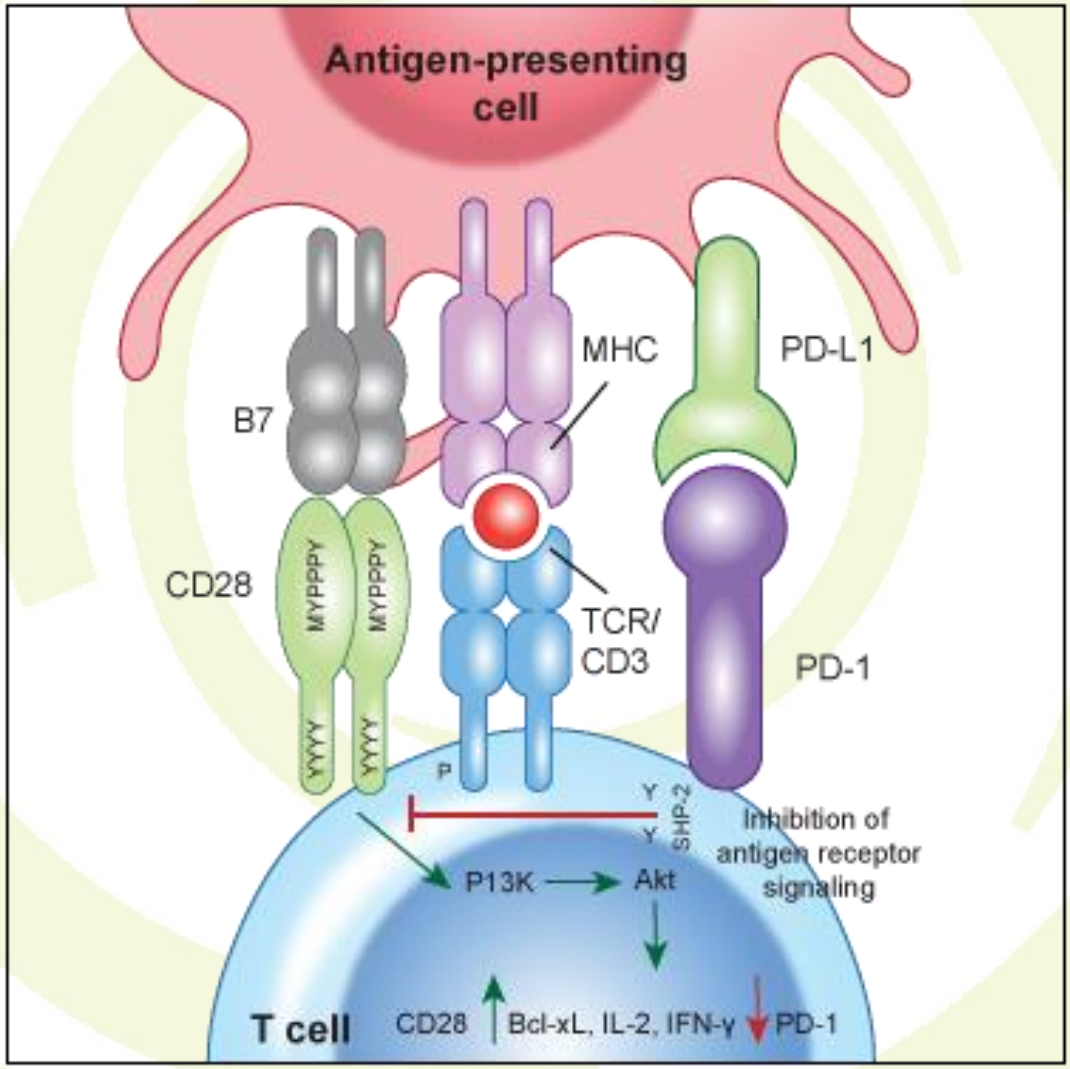
Blocking PD-1/PD-L1 Pathway Reactivates T cells

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



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



Knockout of PD-1 genes associated with autoimmune diseases (preclinical data)

Mice lacking PD-1: autoimmunity depending on model
e.g., arthritis and cardiomyopathy.

Adapted from Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

Polymorphism ofPD-1 genes associated with autoimmune diseases (clinical data)

Autoimmune Disease	Polymorphism
Lupus	PD-1
Rheumatoid Arthritis	PD-1

Adapted from Michot JM, *et al* ; *European Journal of Cancer*; 2016; **54**:139

ADVANCES IN Cancer IMMUNOTHERAPY™

Overview of possible mechanisms of irAE

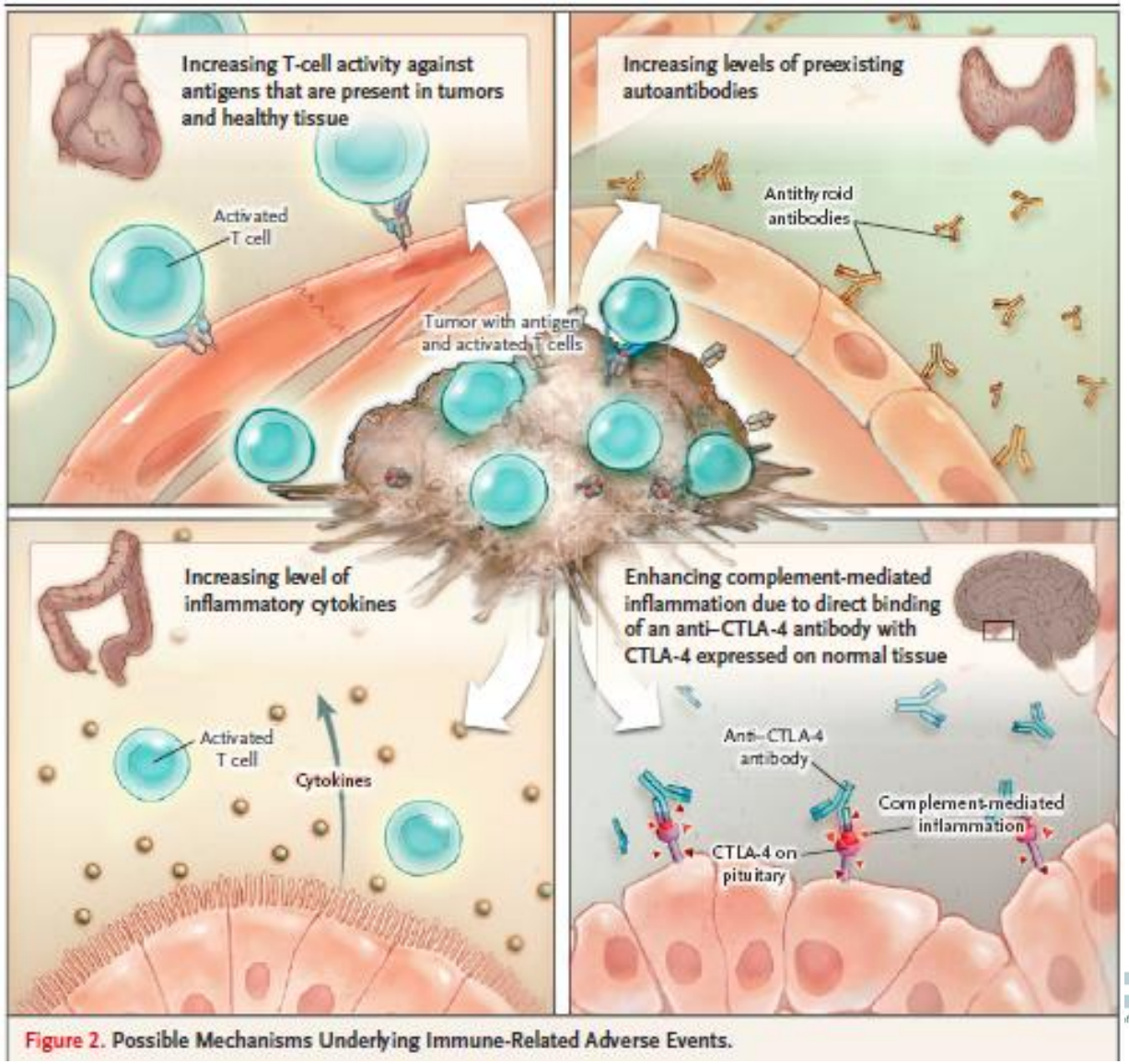


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

N Engl J Med. 2018;378(2):158-168.

ACCC of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Early and late irAEs may occur by distinct mechanisms

Early and common

Mucosal
Colitis
Rash
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

T cell or antibody mediated tissue destruction

Summary: CTLA-4 and PD-1 are important in maintenance of peripheral immune tolerance

- 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
- PD-1 activates regulatory T cells to maintain peripheral tolerance
- Humans with CTLA-4 haploinsufficiency develop a spectrum of autoimmune manifestations similar to irAEs seen after treatment with Ipilimumab