ADVANCES IN Cancer IMMUNOTHERAPY™

Mechanisms of Immune-Related Adverse Events

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- Clinical Trials Advisory Board, Eli Lilly

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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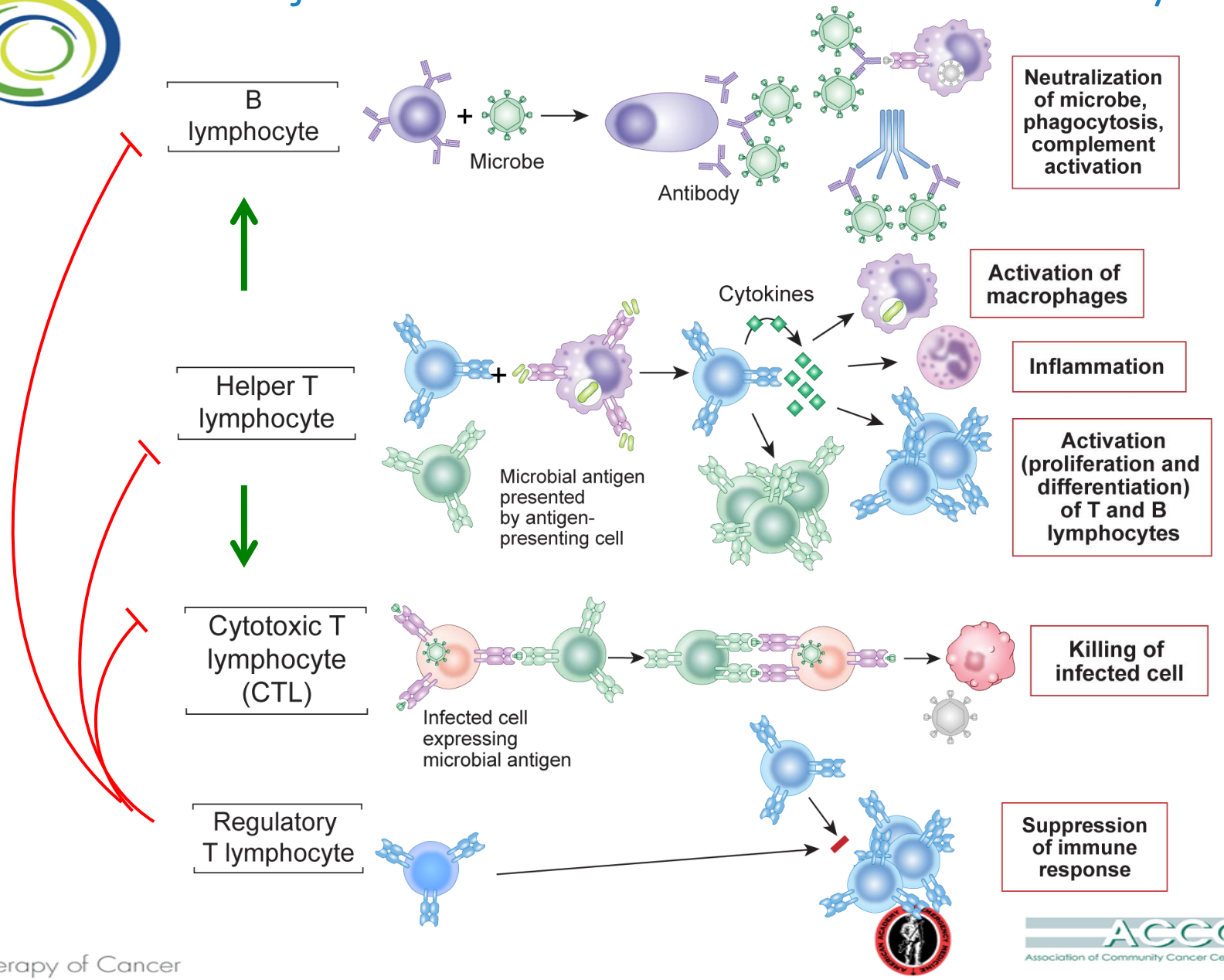
Major Effector Cells of the Immune System



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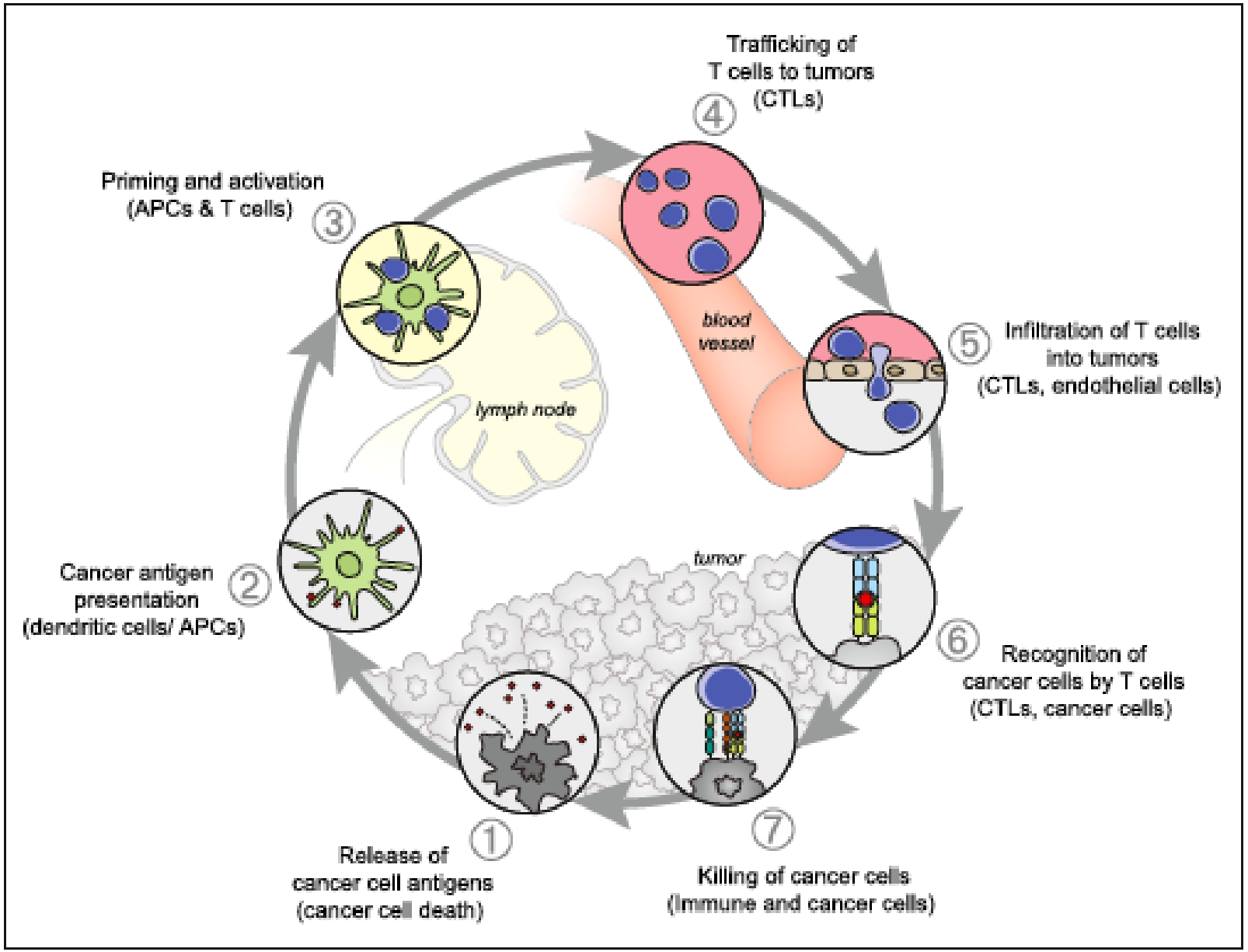
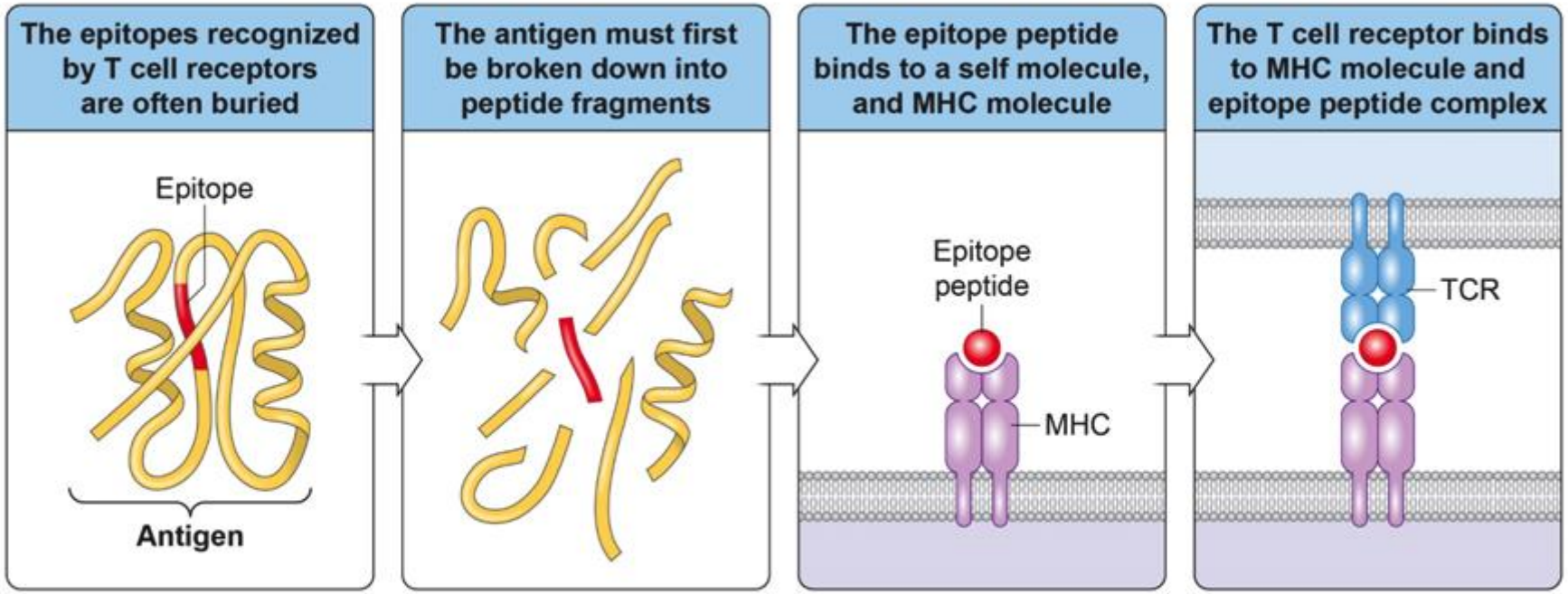


As a reminder…



MHC = Major Histocompatibility Complex

also called the HLA (human leukocyte antigen) complex

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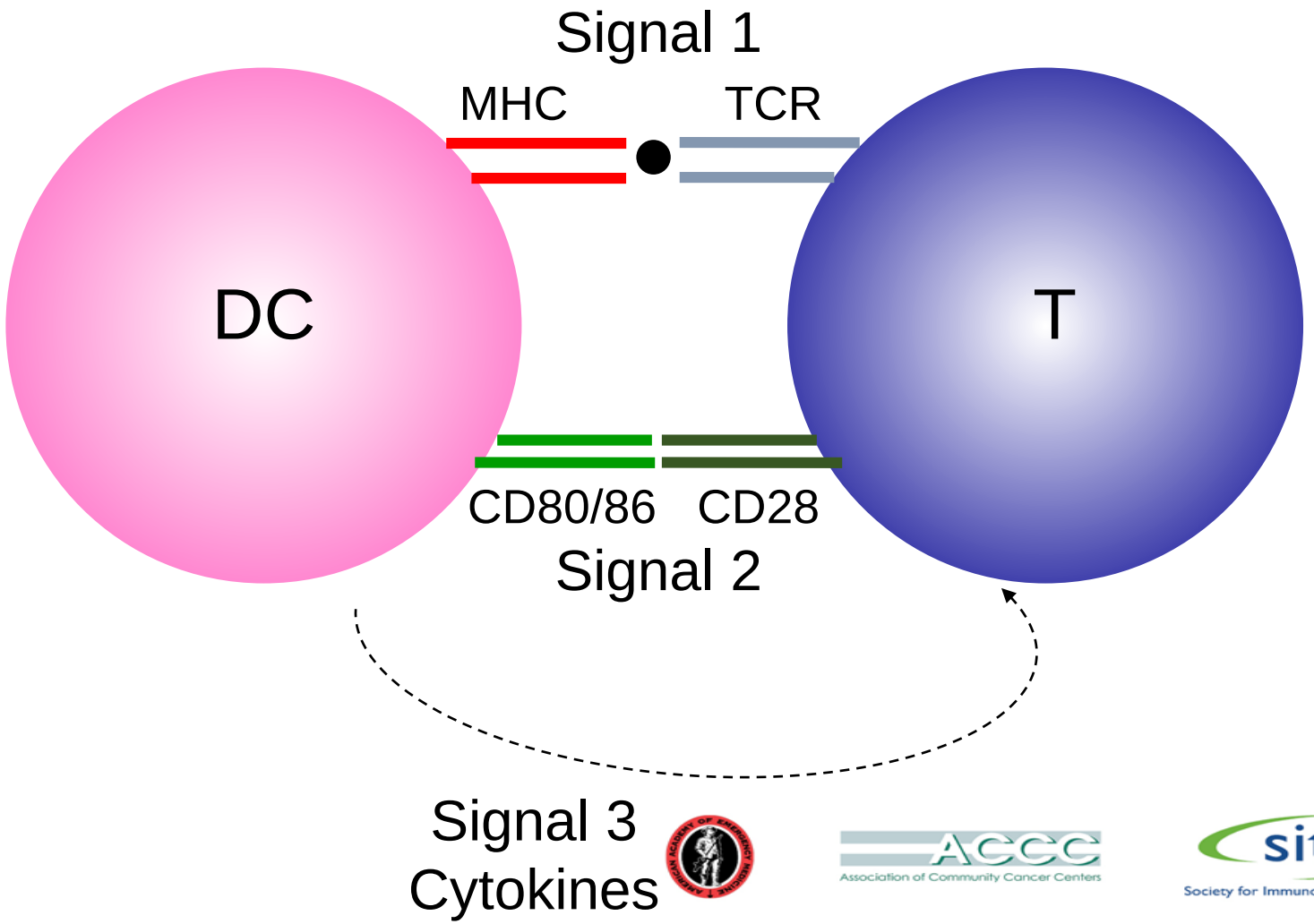
T cells normally require two signals for full activation. The first signal consists of antigen in context of HLA/MHC that is detected by the T cell receptor (TCR). The second required signal is what is termed "co-stimulation" that is provided through interaction of B7 molecules on antigen presenting cells with CD28 on the T cells.

B7 is upregulated by inflammatory cytokines that are made when antigen presenting cells and macrophages detect an active infection. In the absence of such signals, the T cell will only get the TCR signal, which leads to a non-functional state.



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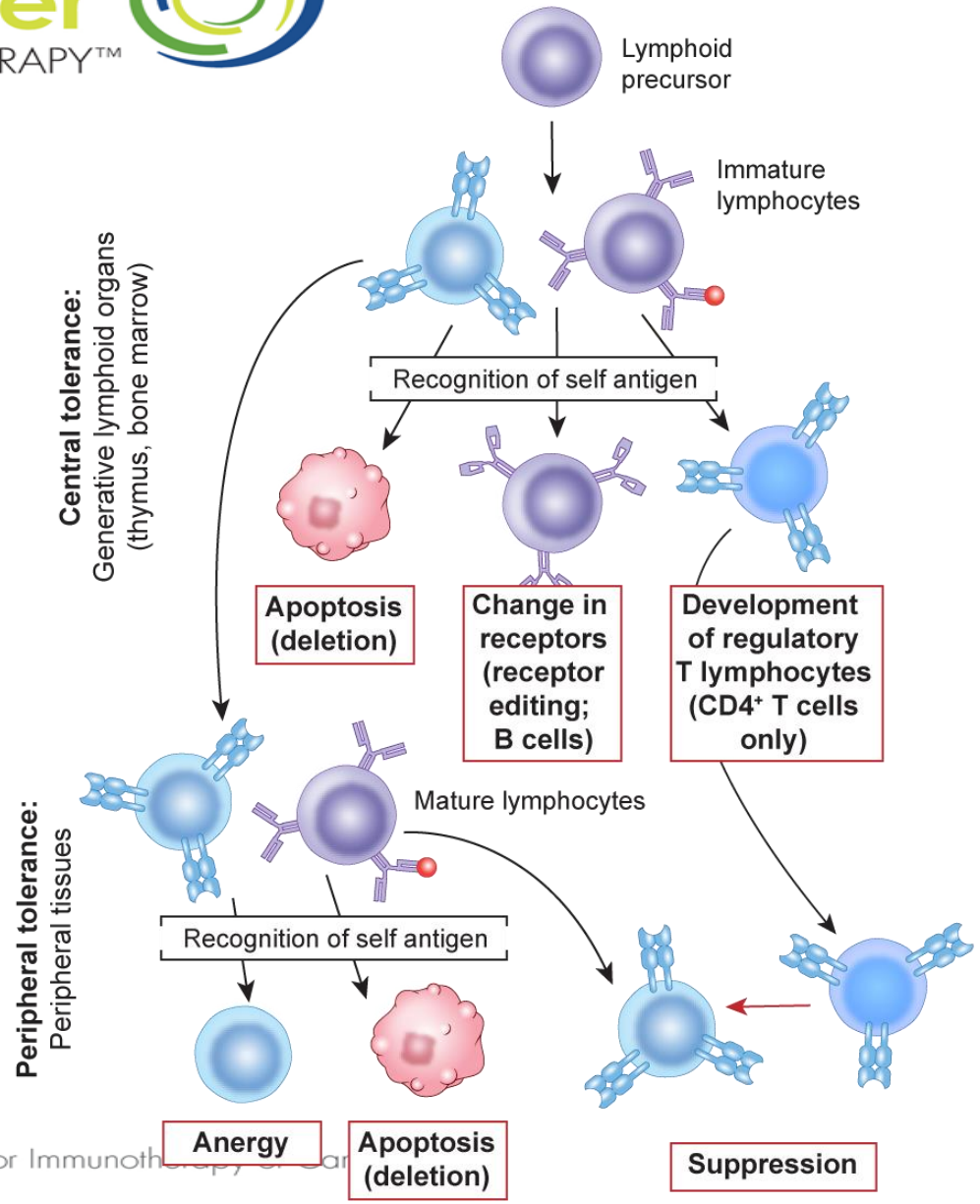
Most Autoimmune Diseases are due to <u>Failure of T cell Tolerance</u>

Immunologic Tolerance: unresponsiveness of immune system to self antigens

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

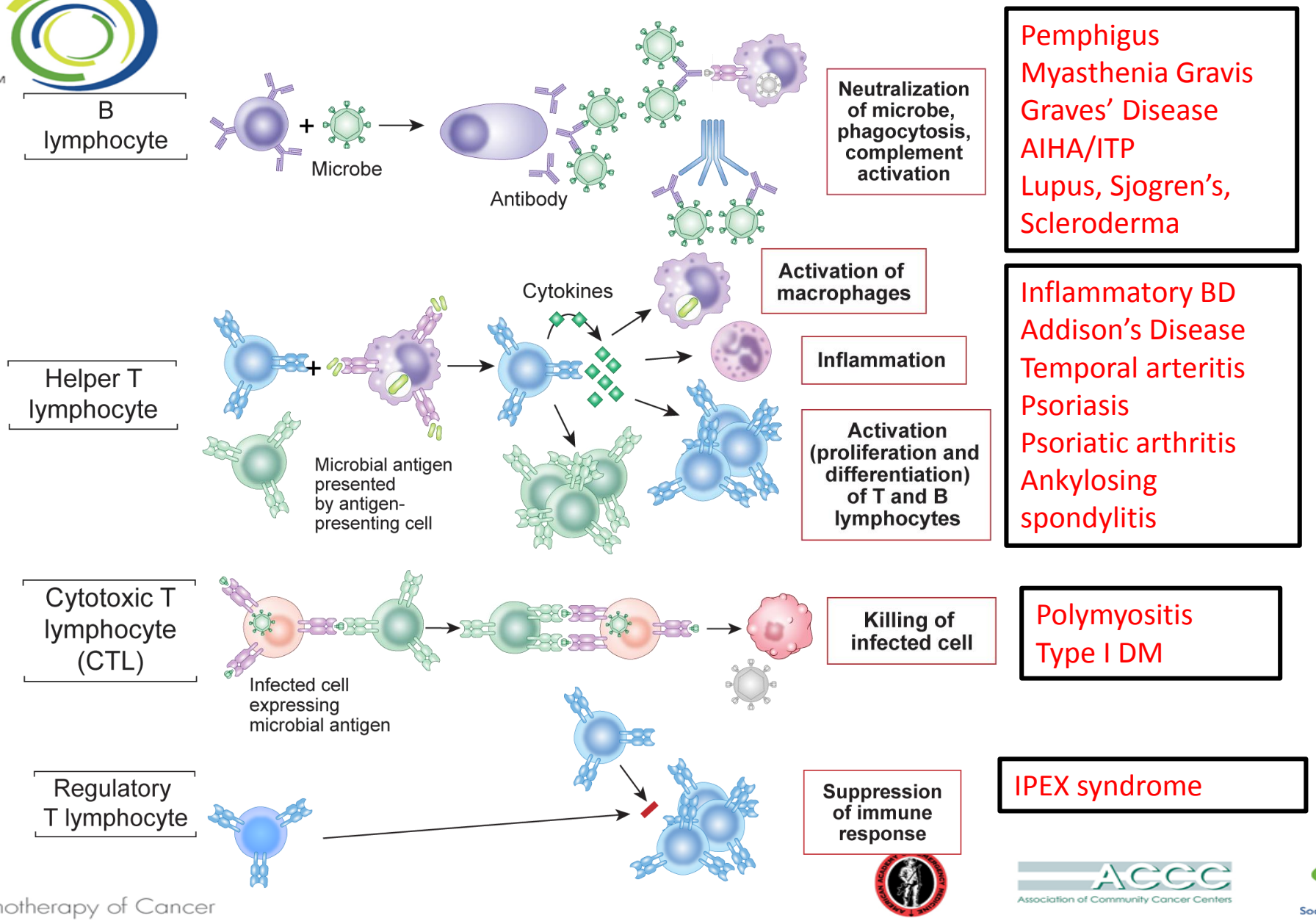
- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (anergic)

HLA (or MHC) is the strongest genetic factor for susceptibility to autoimmune disease

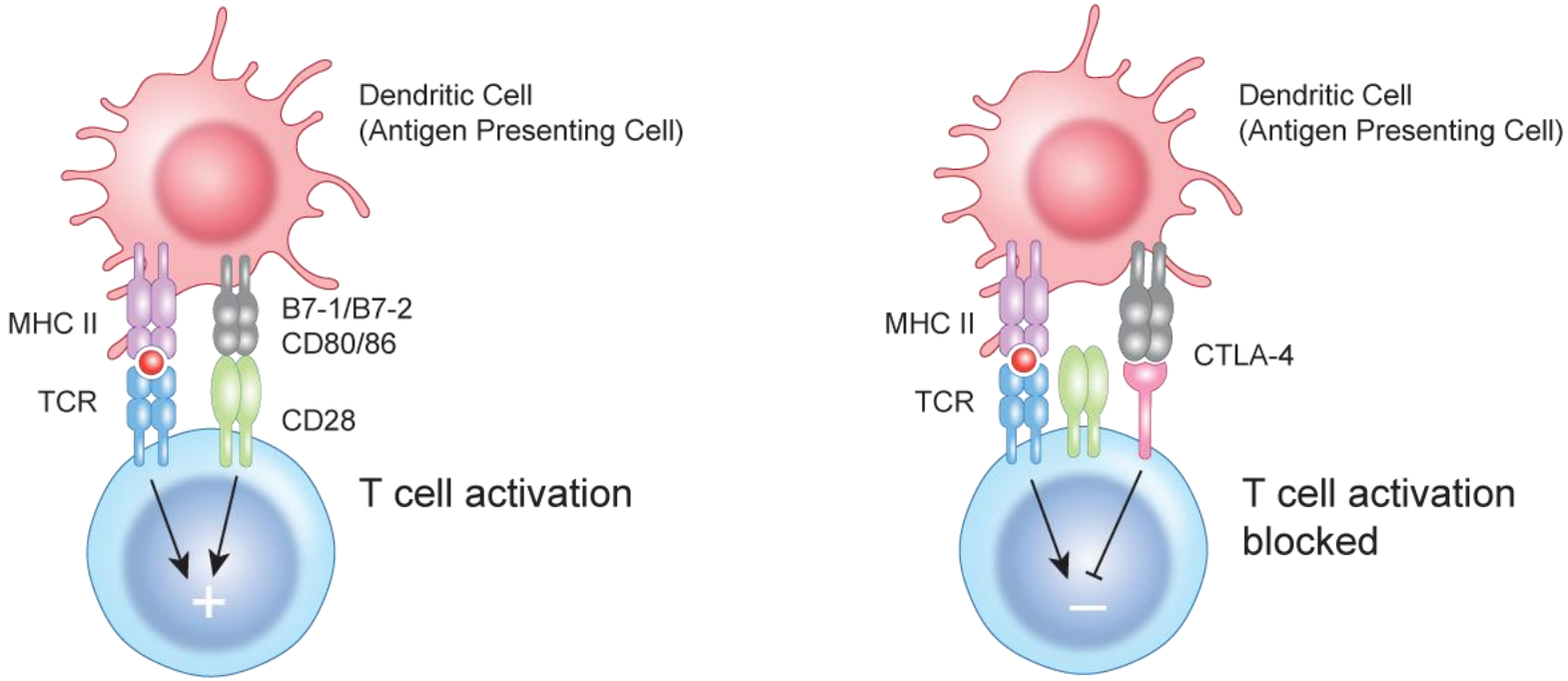
HLA- and gender-associated risk for autoimmune disease			
Disease	**HLA allele**	**Relative risk**	**Sex ratio (♀:♂)**
Ankylosing spondylitis	B27	87.4	0.3
Type 1 diabetes	DQ2 and DQ8	~25	~1
Goodpasture's syndrome	DR2	15.9	~1
Pemphigus vulgaris	DR4	14.4	~1
Autoimmune uveitis	B27	10	<0.5
Psoriasis vulgaris	CW6	7	~1
Systemic lupus erythematosus	DR3	5.8	10–20
Addison's disease	DR3	5	~13
Multiple sclerosis	DR2	4.8	10
Rheumatoid arthritis	DR4	4.2	3
Graves' disease	DR3	3.7	4–5
Hashimoto's thyroiditis	DR5	3.2	4–5
Myasthenia gravis	DR3	2.5	~1
Type I diabetes	DQ6	0.02	~1

Figure 15.37 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

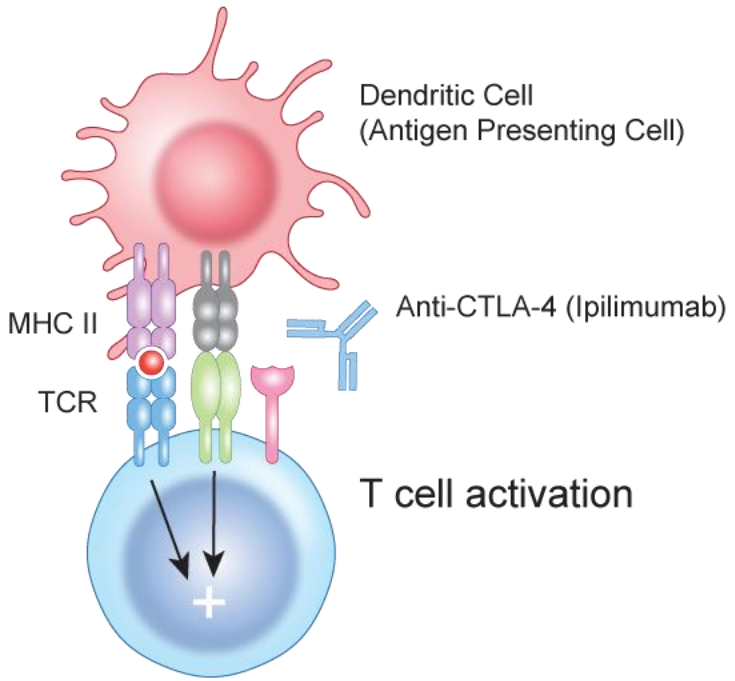
Major Effector Cells of the Immune System

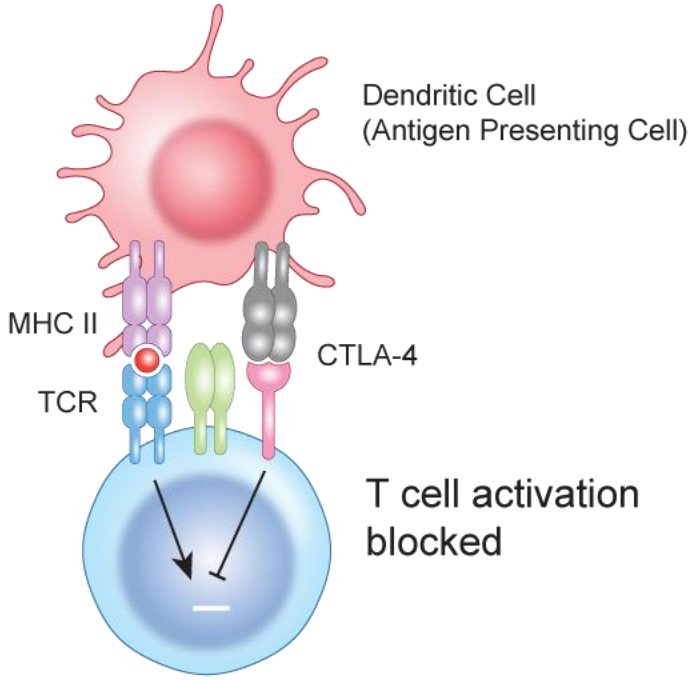


CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules



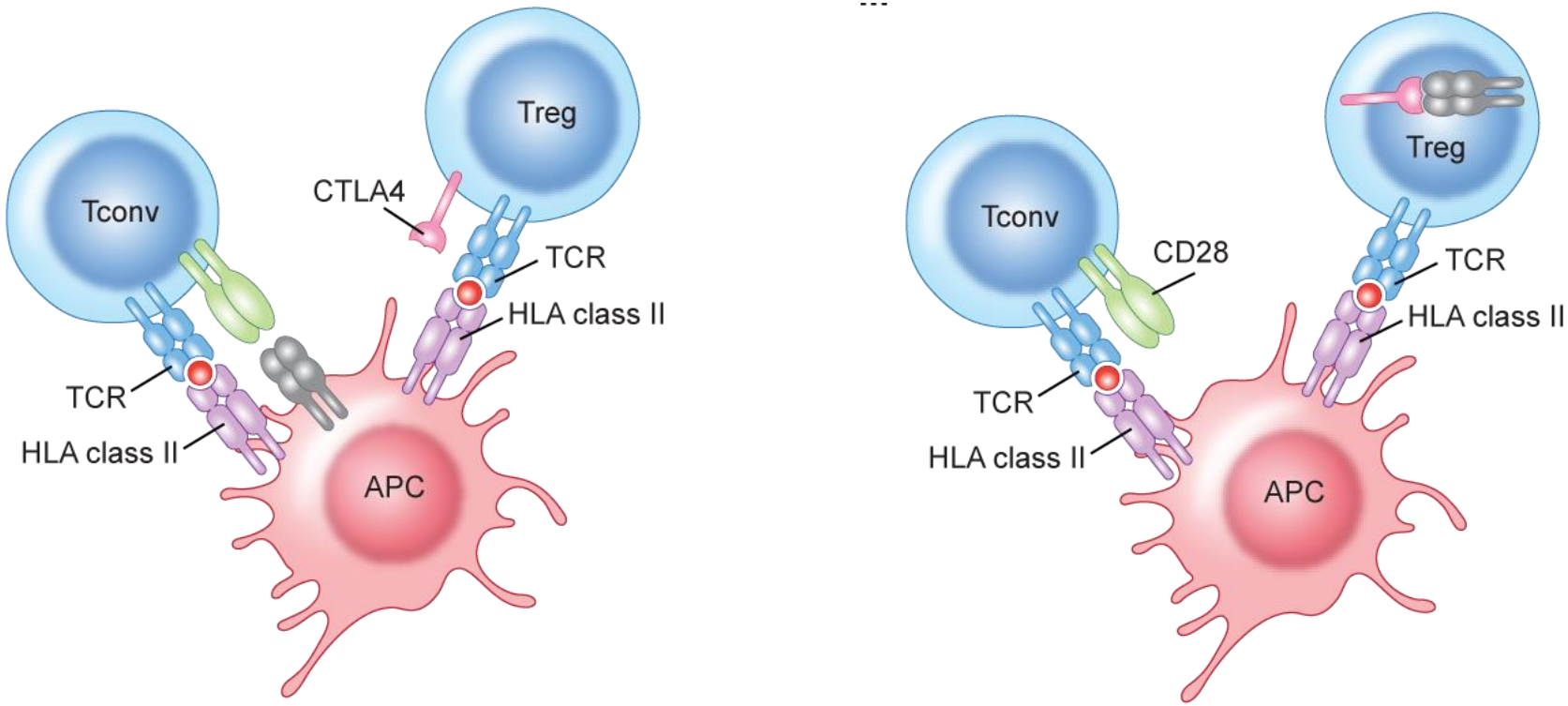
Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation





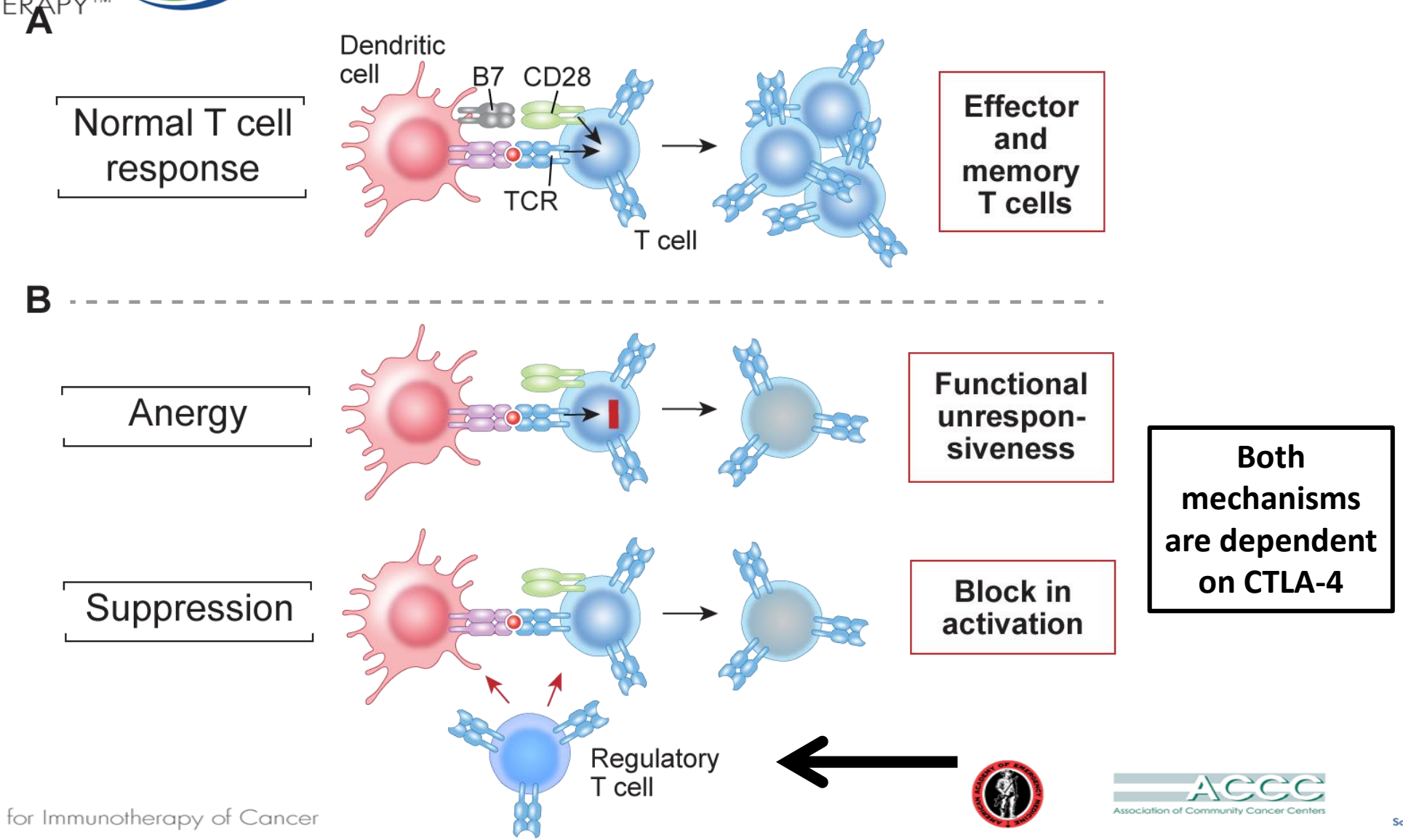
Breakdown of peripheral tolerance leading to activation of self-reactive T cells

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

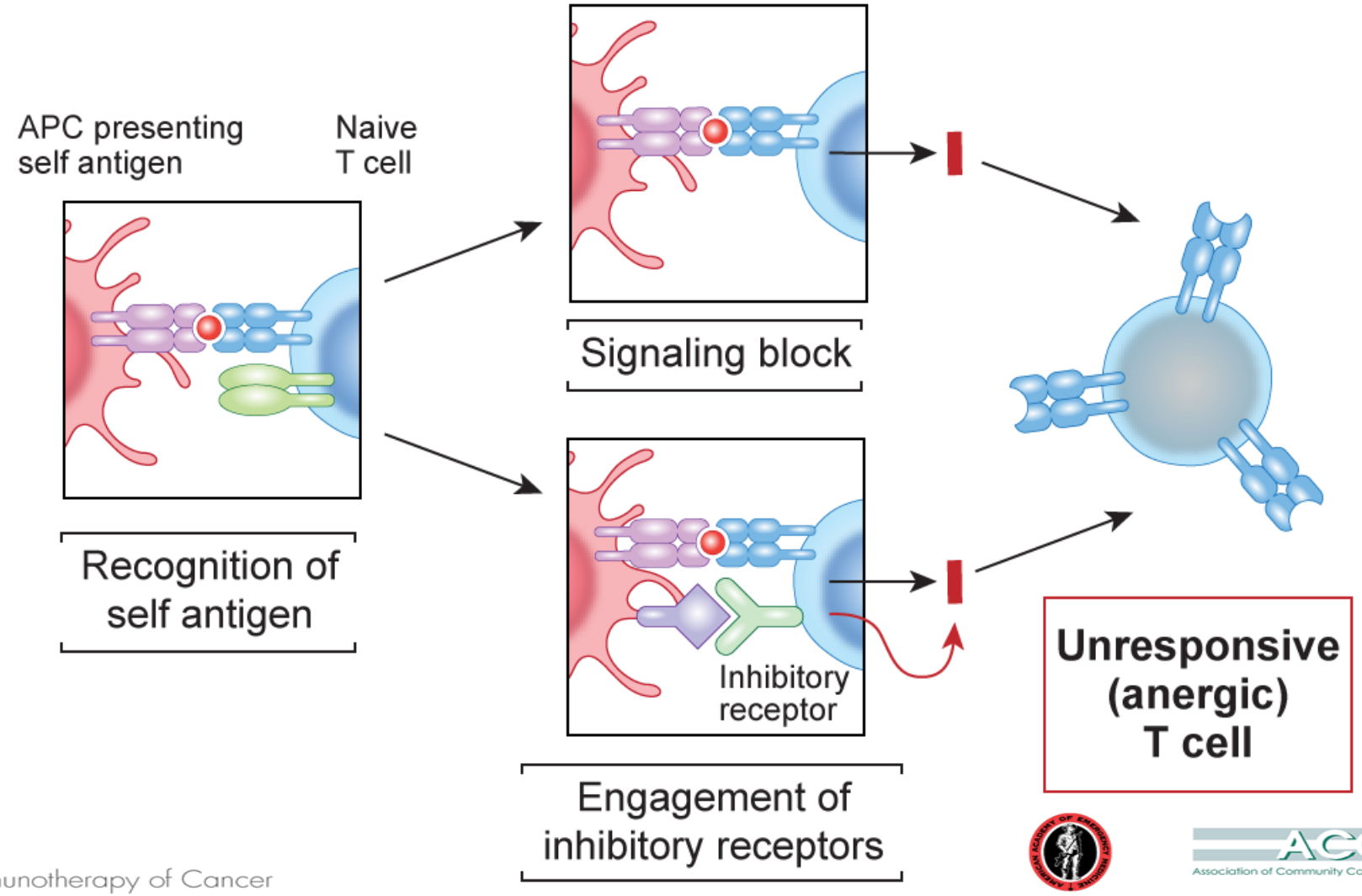


Anti-CTLA-4 (ipilimumab) may interfere with inhibitory function of Tregs

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

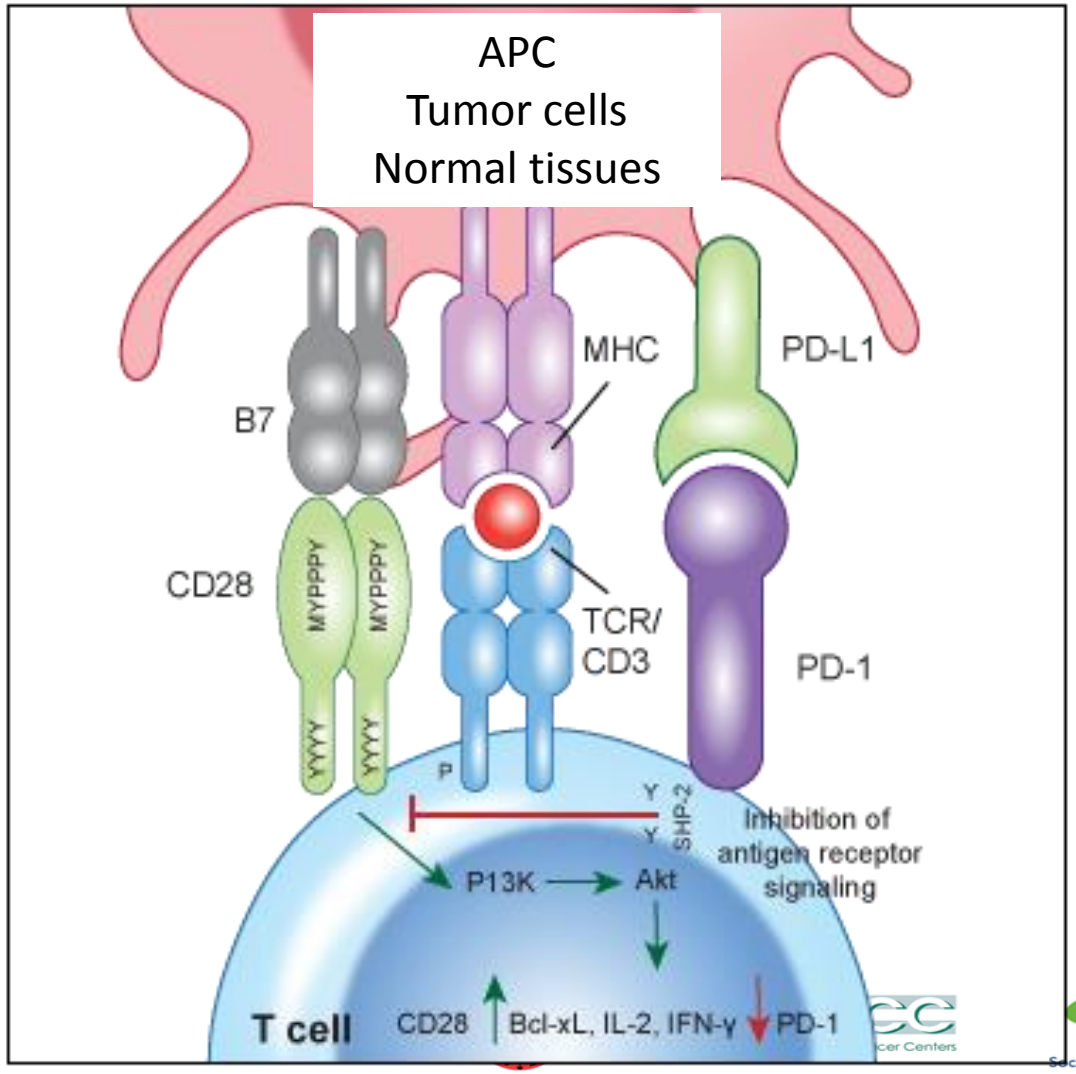


Inhibitory receptors provide a second mechanism for maintenance of tolerance



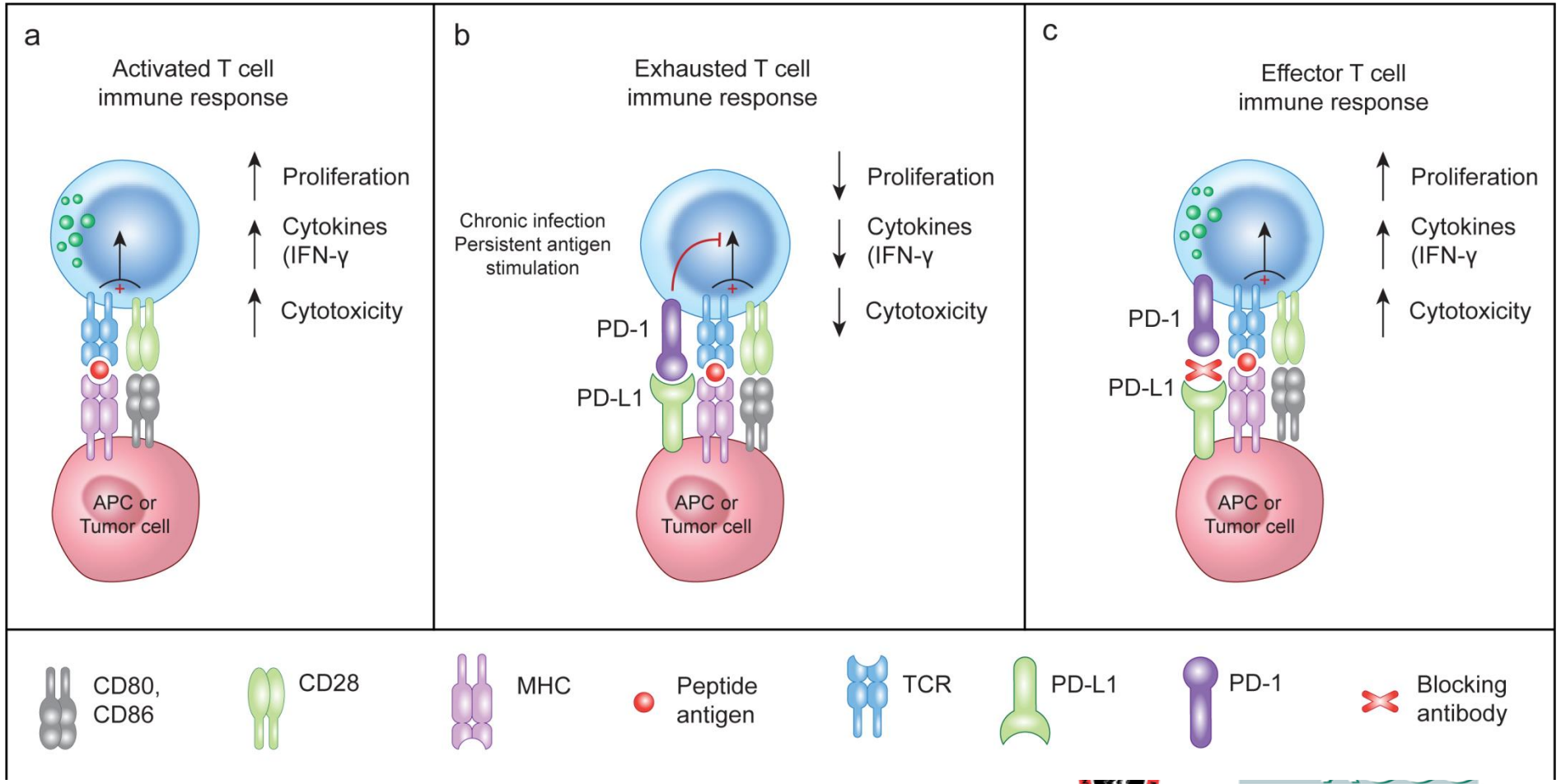
Interaction of PD-1 with its ligands, PD-L1/PD-L2 inhibits CD28 signaling in T cells

- 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



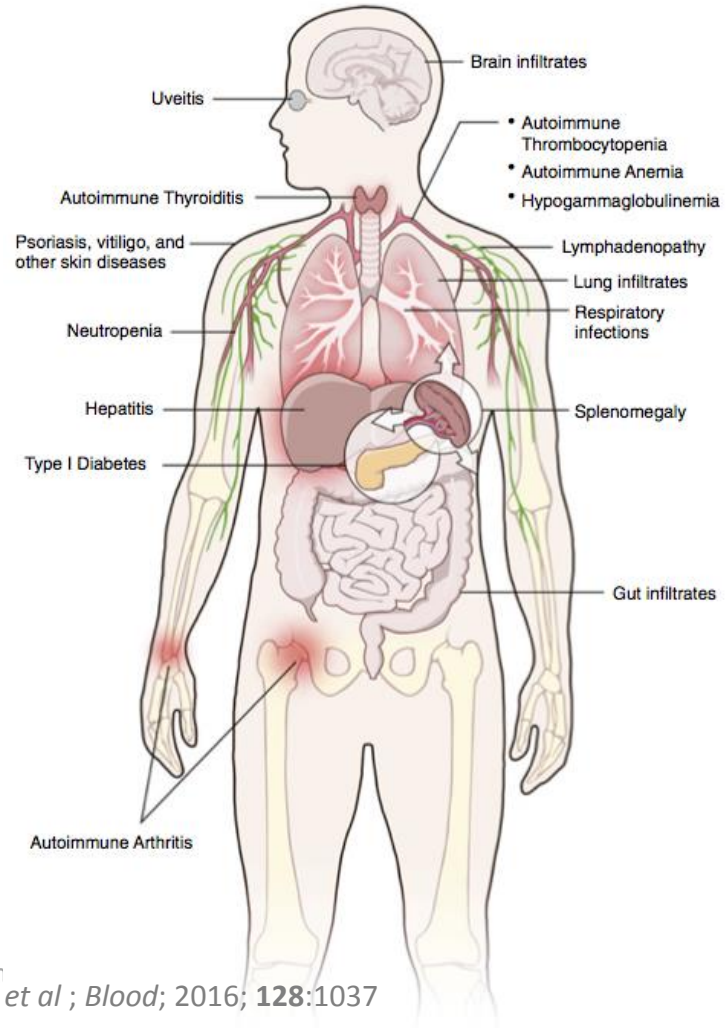
Polymorphisms in CTLA-4 and PD-1 genes have been linked to human autoimmune diseases

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; PD-1
Rheumatoid Arthritis	CTLA-4; PD-1
Addison's disease	CTLA-4

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

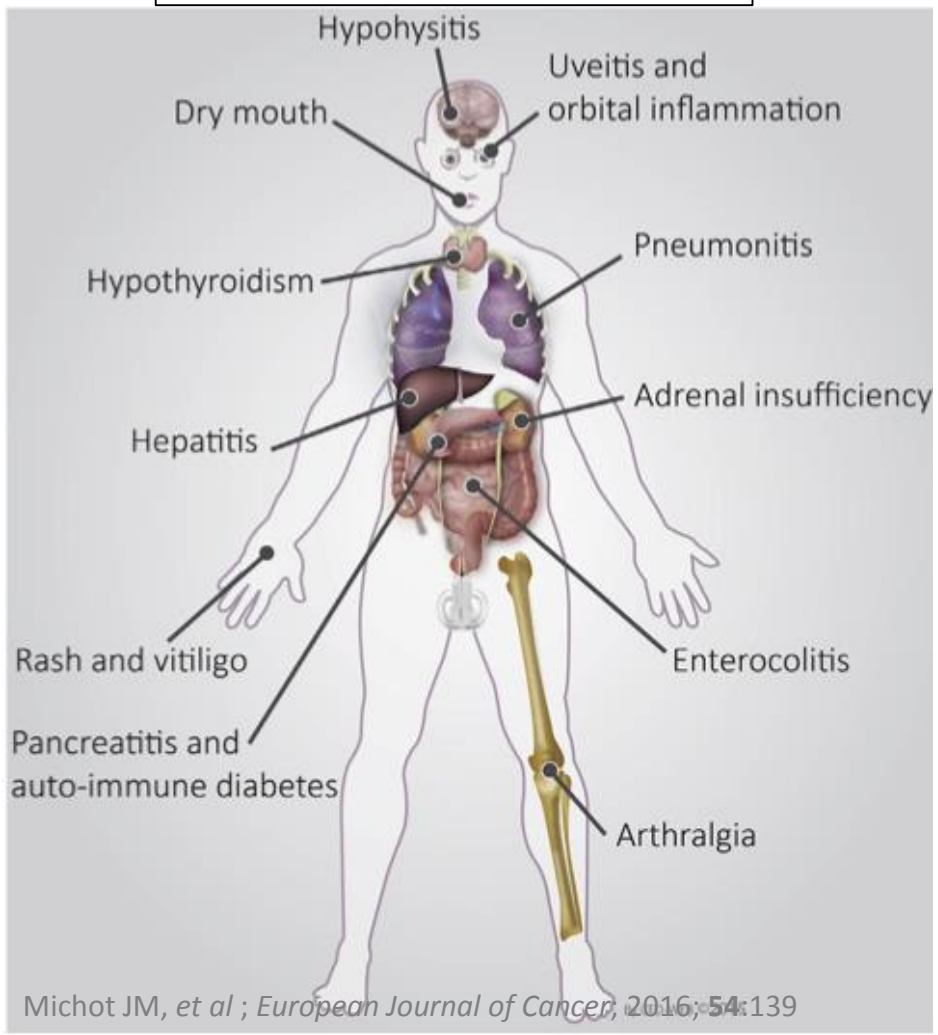
People with CTLA-4 haploinsufficiency develop a spectrum of autoimmune diseases similar to the irAEs observed with ipilimumab

CHAI/LATAIE Phenotype



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

Ipilimumab irAEs



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

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