

ADVANCES IN  
**Cancer**  
IMMUNOTHERAPY™



# Mechanisms of Immune-Related Adverse Events

Rolf A. Brekken, PhD  
Professor

UT Southwestern Medical Center



Society for Immunotherapy of Cancer

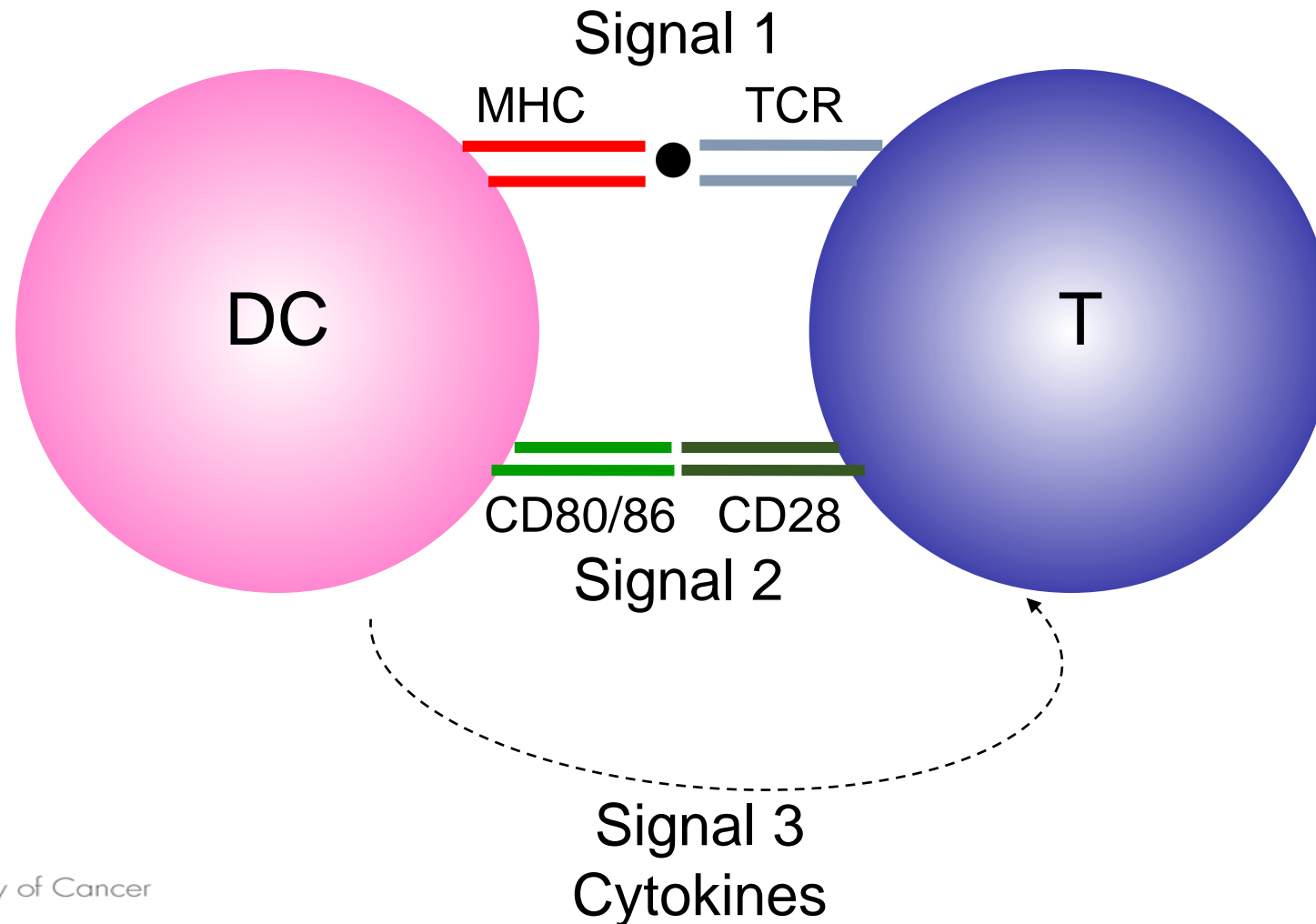
# Disclosures

- No relevant financial relationships to disclose

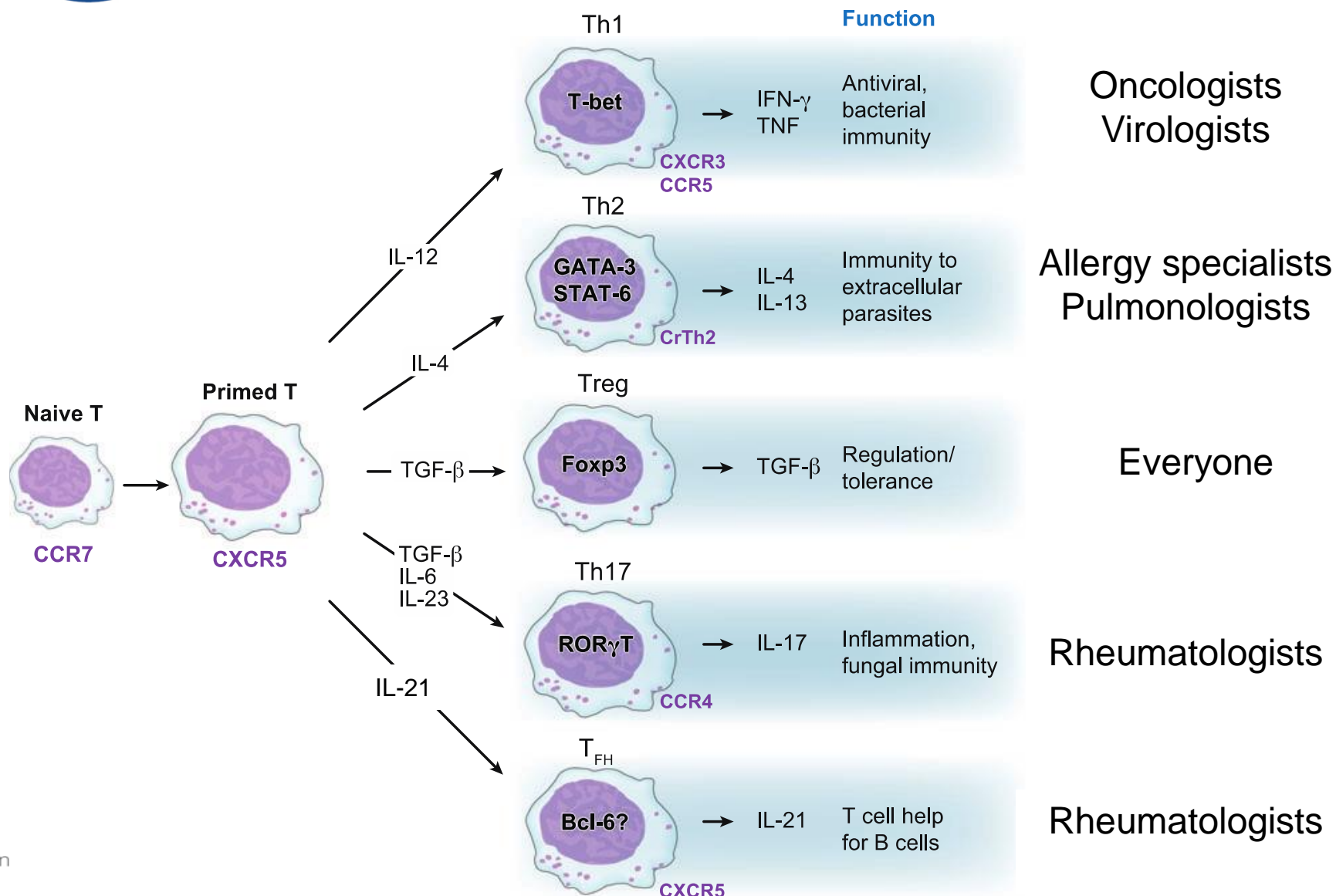
## Outline

- 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

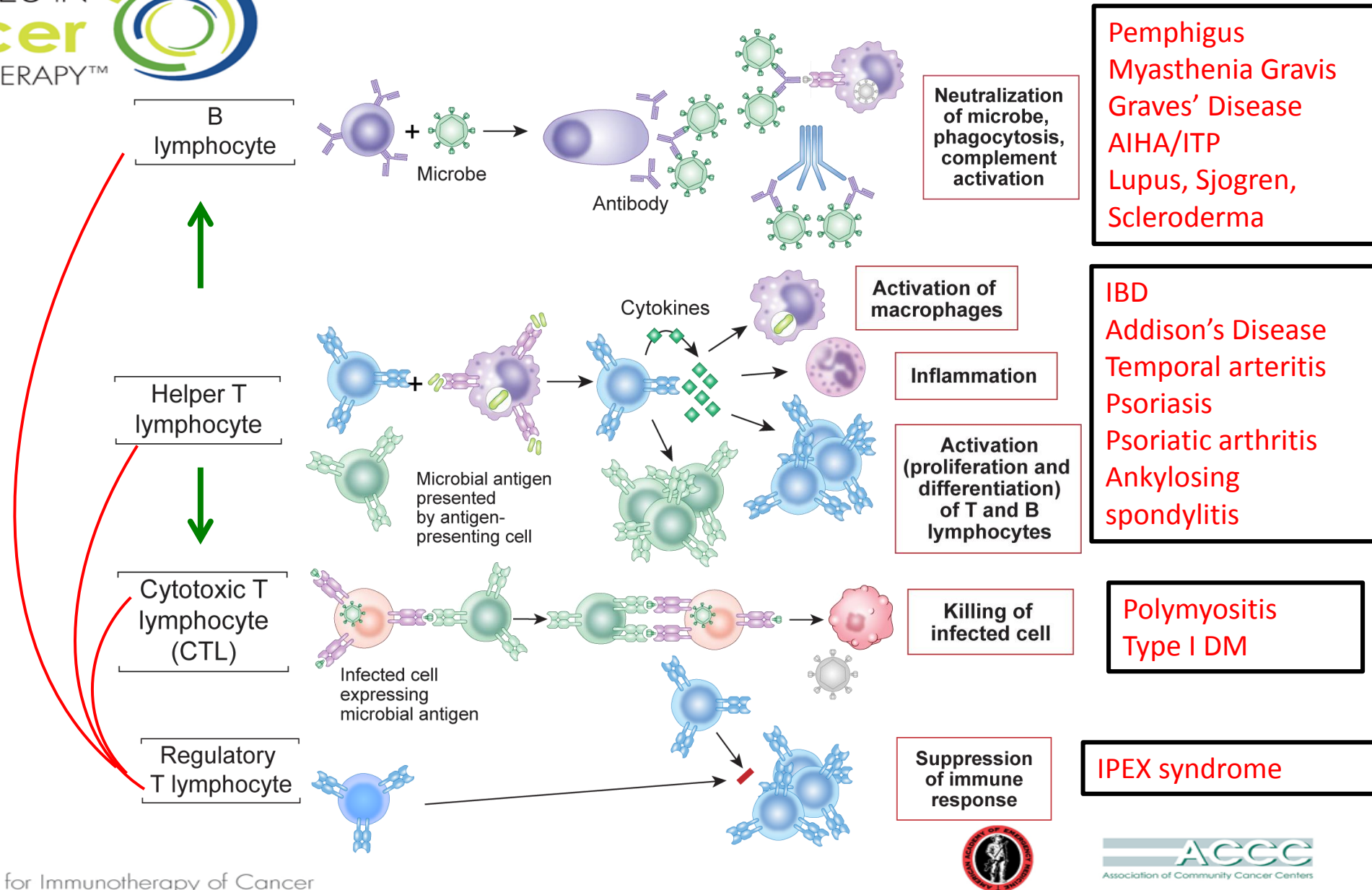
# For full T cell activation and differentiation, T cells need 3 signals



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



# Major Effector Cells of the Immune System

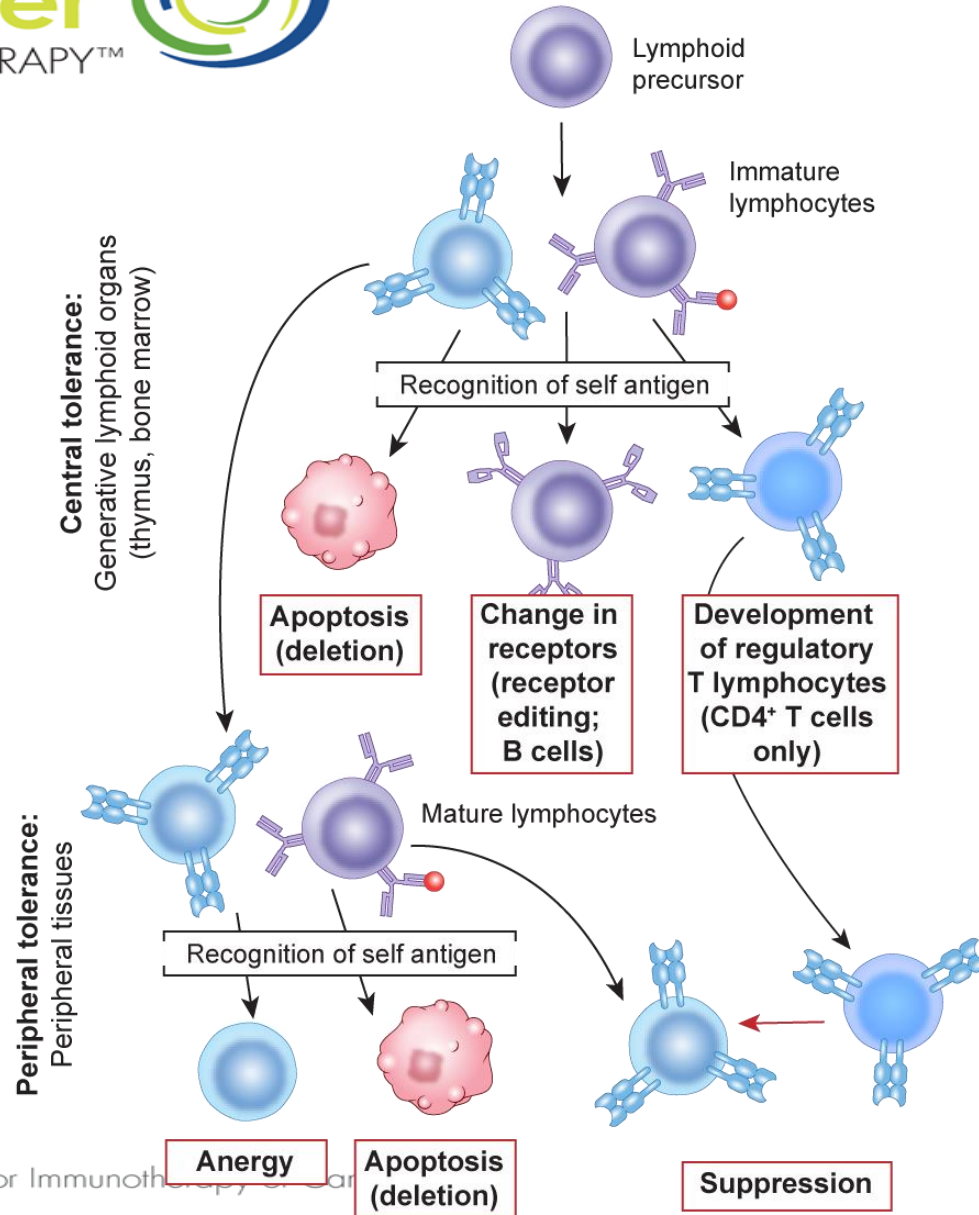


## Most Autoimmune Diseases are due to Failure of T cell Tolerance

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

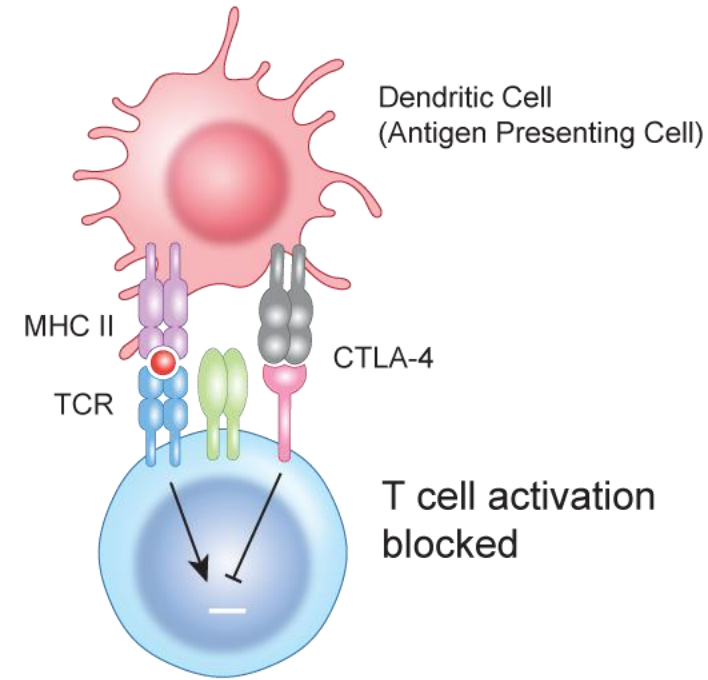
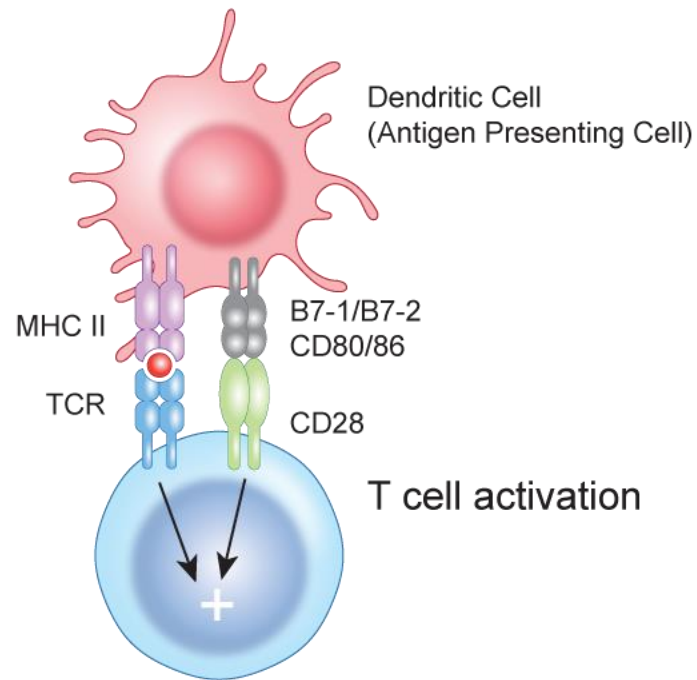
## Peripheral Tolerance

- 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)

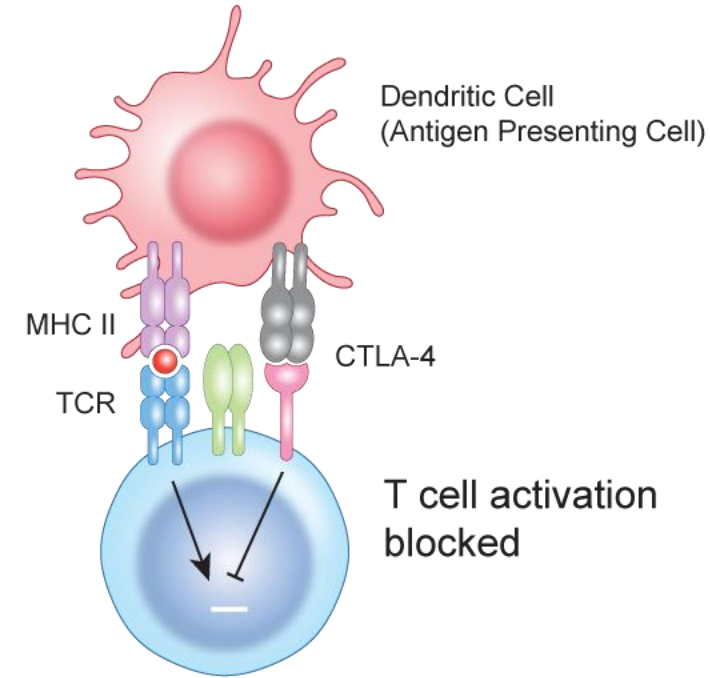
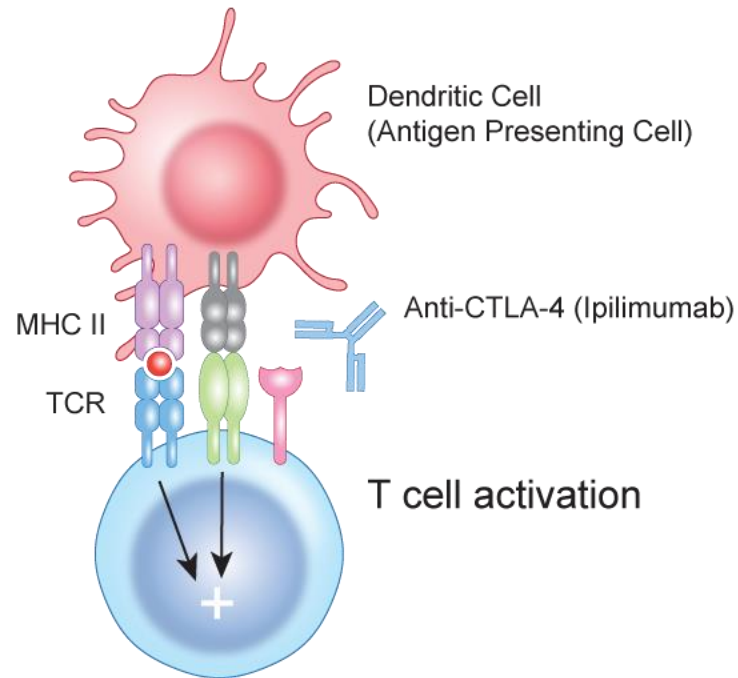




# CTLA-4 inhibits co-stimulation by blocking interaction between CD28 and B7 molecules

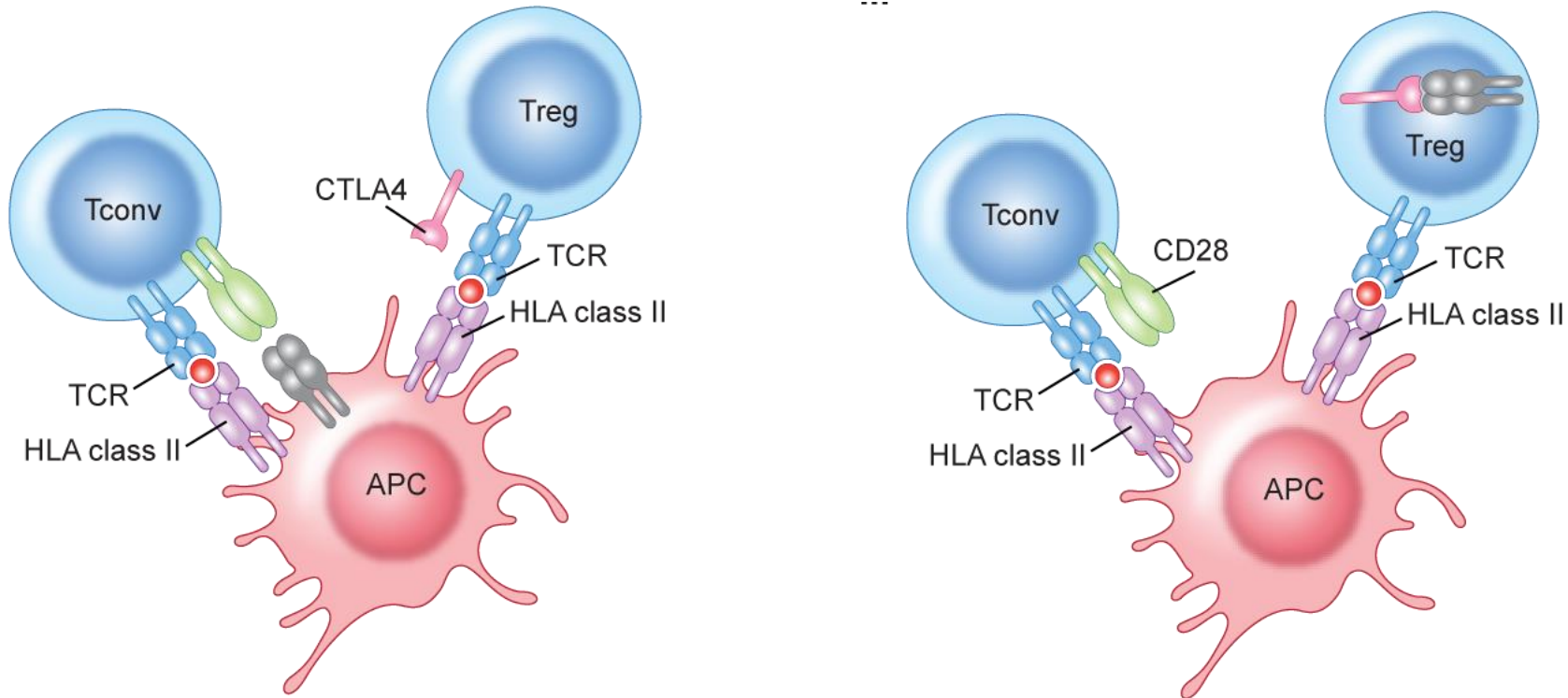


# Anti-CTLA-4 can lead to breakdown of peripheral tolerance by restoring co-stimulation



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

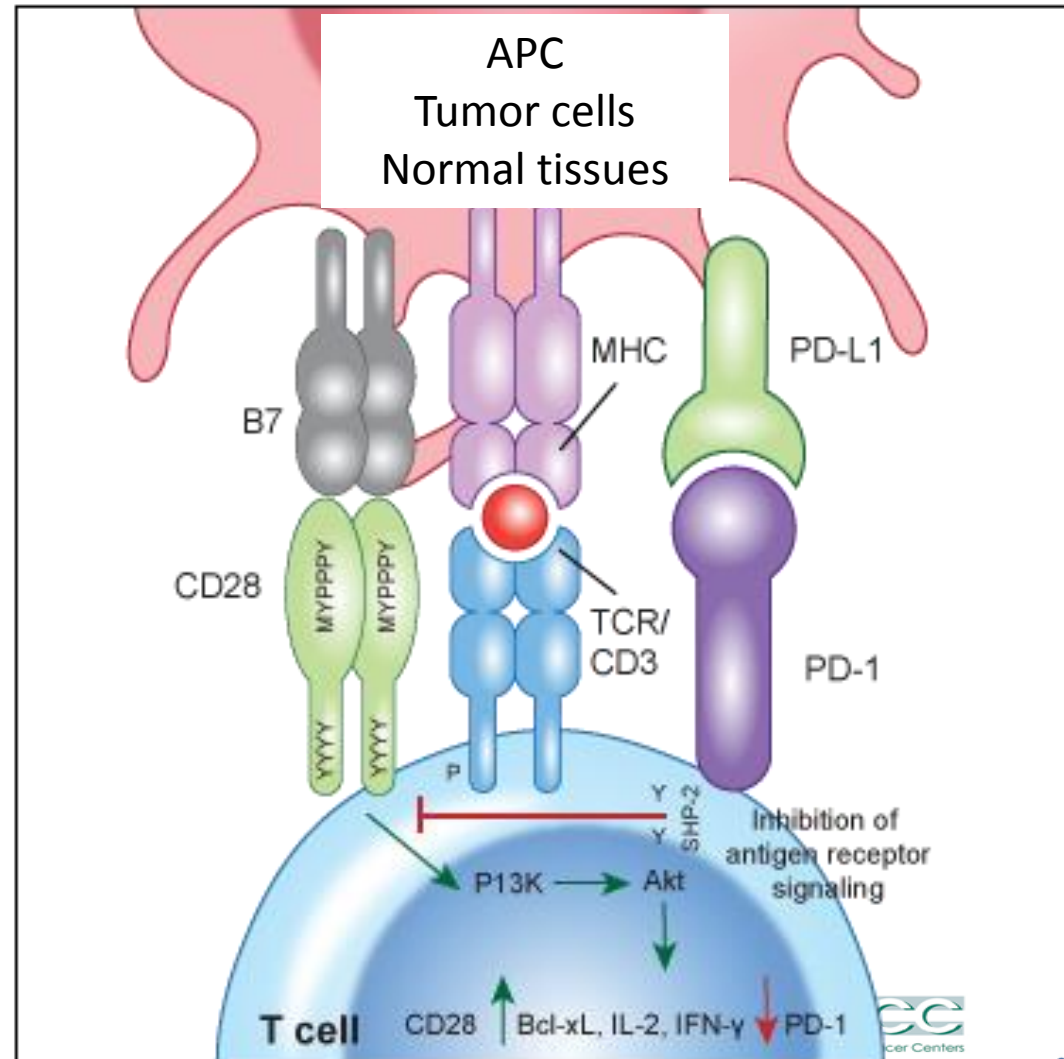
Regulatory T cells (Tregs) use CTLA-4 to remove B7 molecules from surface of antigen presenting cells to prevent activation of self reactive T cells



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



# 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<sub>17</sub>)

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