

Immune Tolerance

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In memory of Dr. Vily Panoutsakopoulou

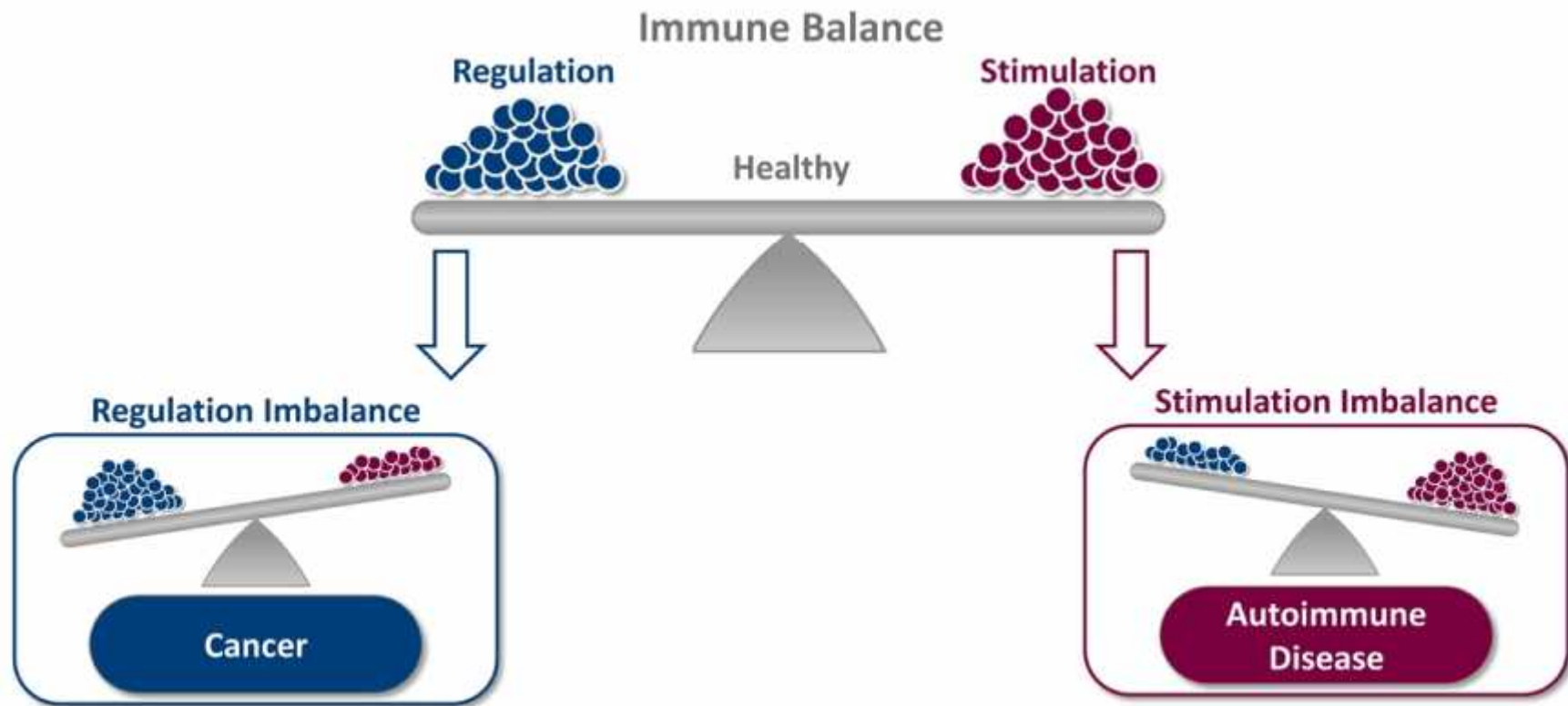


1967-2018

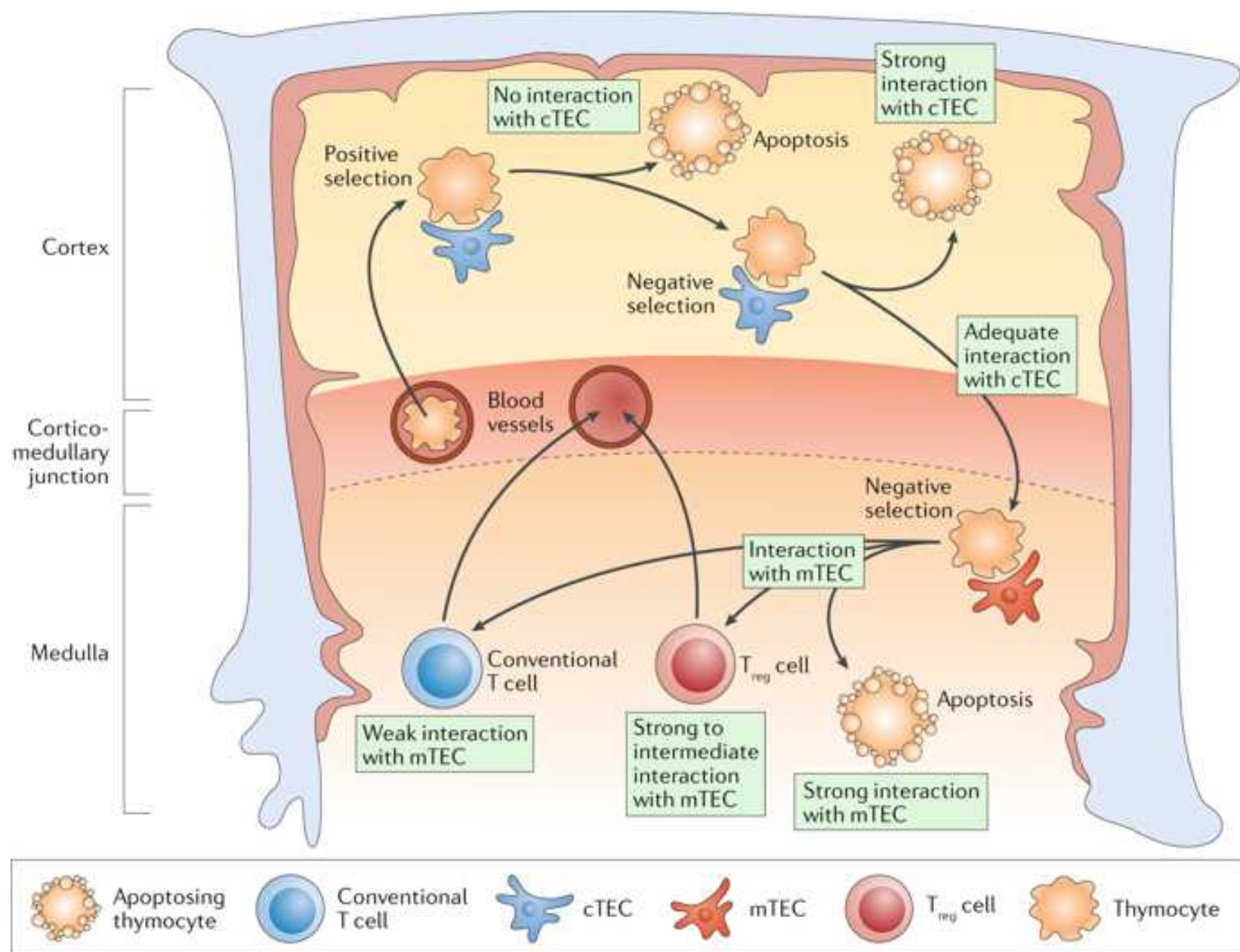
Immune Tolerance: essential for homeostasis and prevention of self recognition



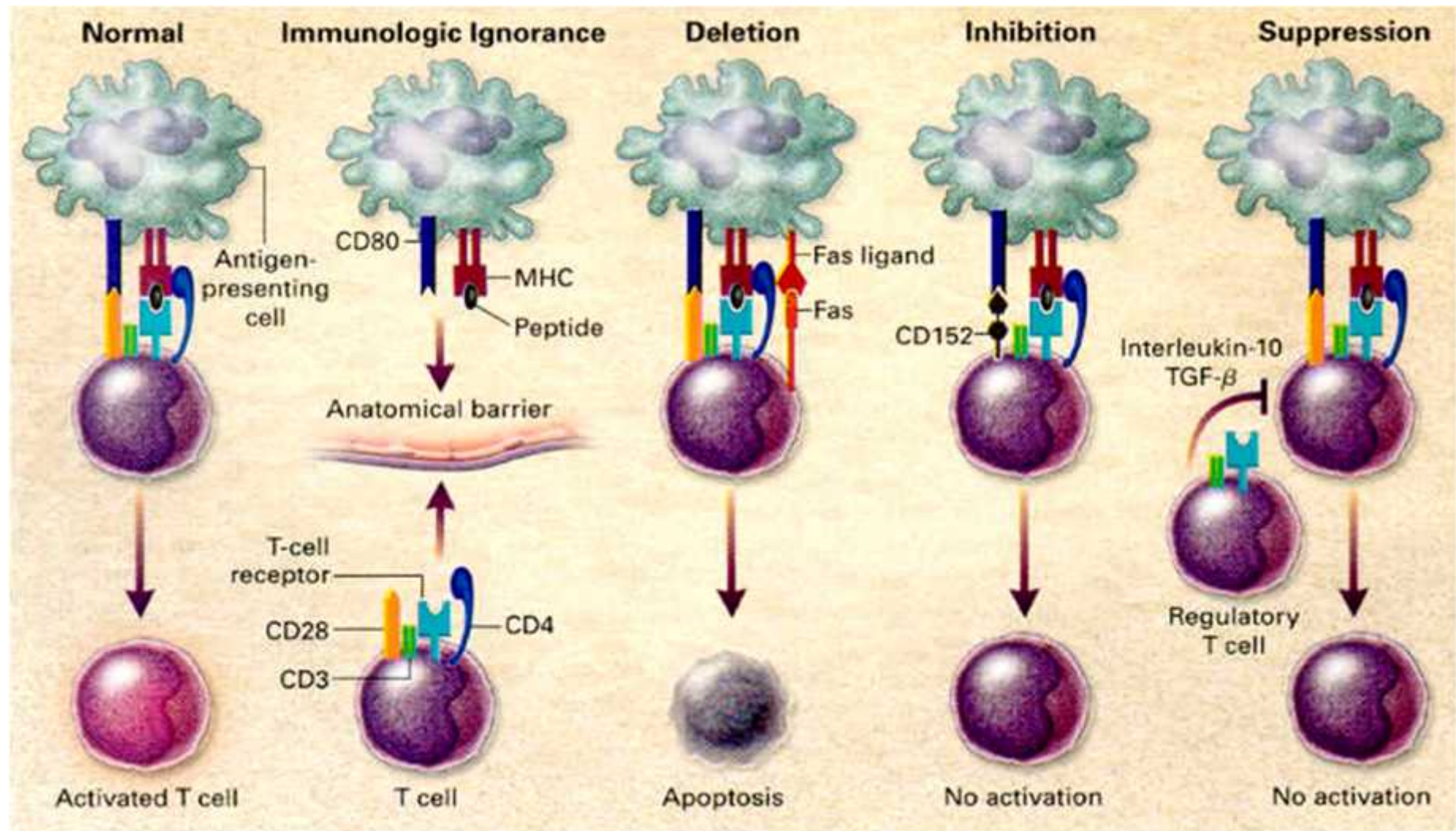
Unbalance of immune tolerance in Autoimmunity and Cancer



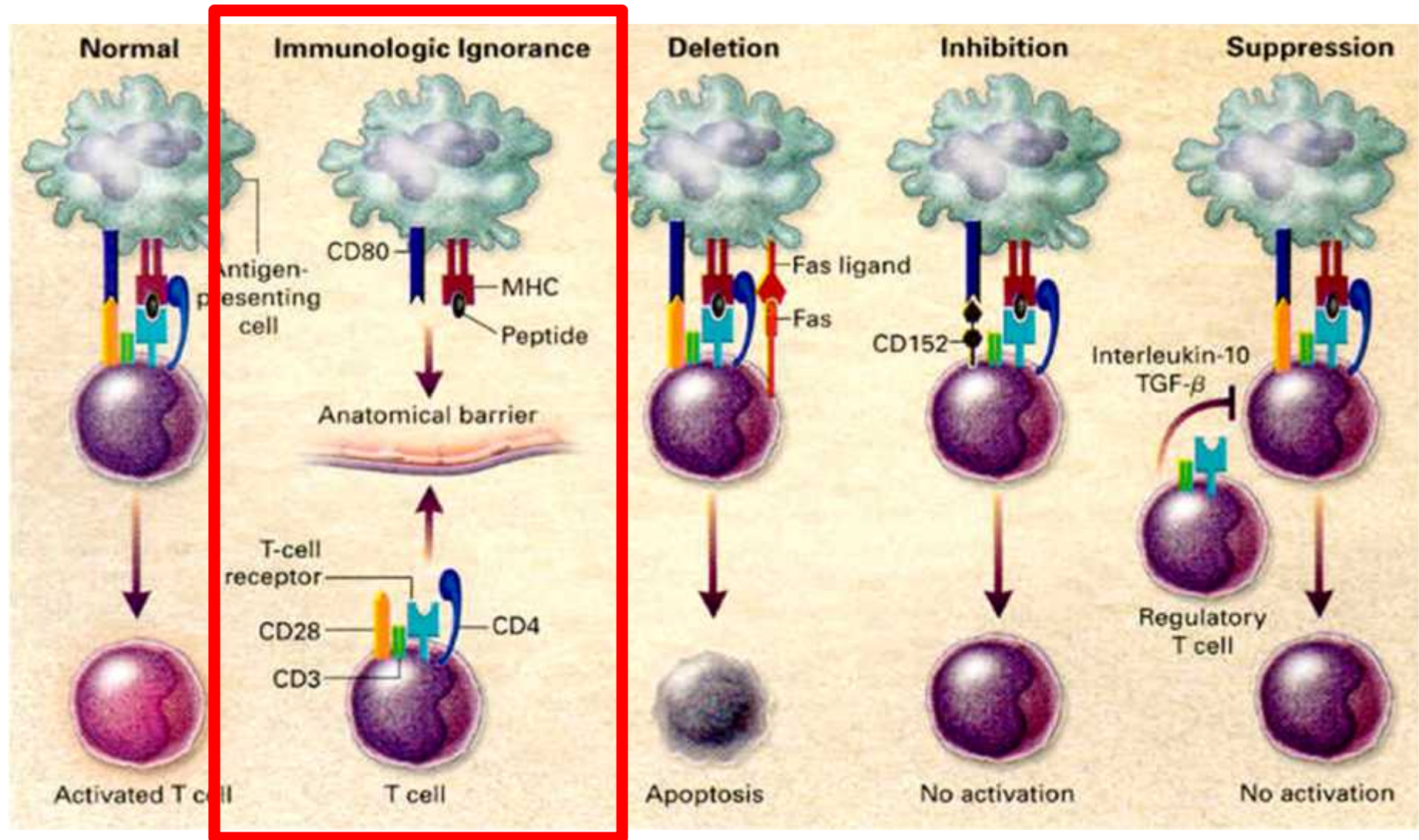
Central tolerance: T cell selection in the thymus



Peripheral mechanisms of tolerance operate to maintain immune homeostasis



Peripheral mechanisms of tolerance operate to maintain immune homeostasis



Immunologic ignorance (the sequestration of self-antigens by autoreactive clones)

Immunologically Privileged sites: Brain, Anterior chamber of eye, Testis and Uterus

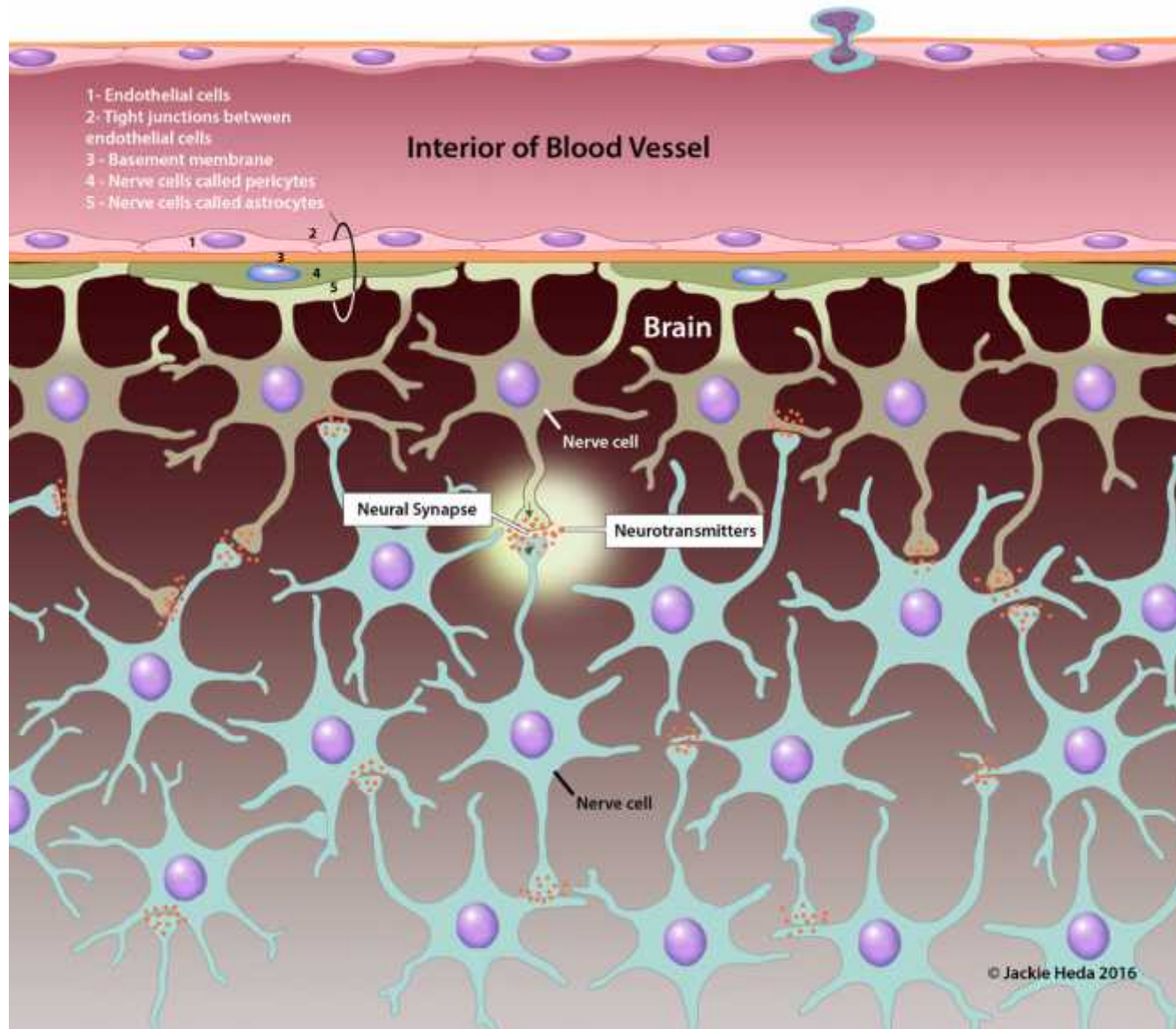
Tissue grafts placed in these sites do not elicit an immune response – **no rejection**

Mechanisms of immunologic ignorance:

- ✓ Lack of lymphatic drainage
- ✓ Presence of physical barriers between blood and tissue
- ✓ secretion of immunosuppressive factors

Anatomical Barriers: The Example of The Blood Brain Barrier (BBB)

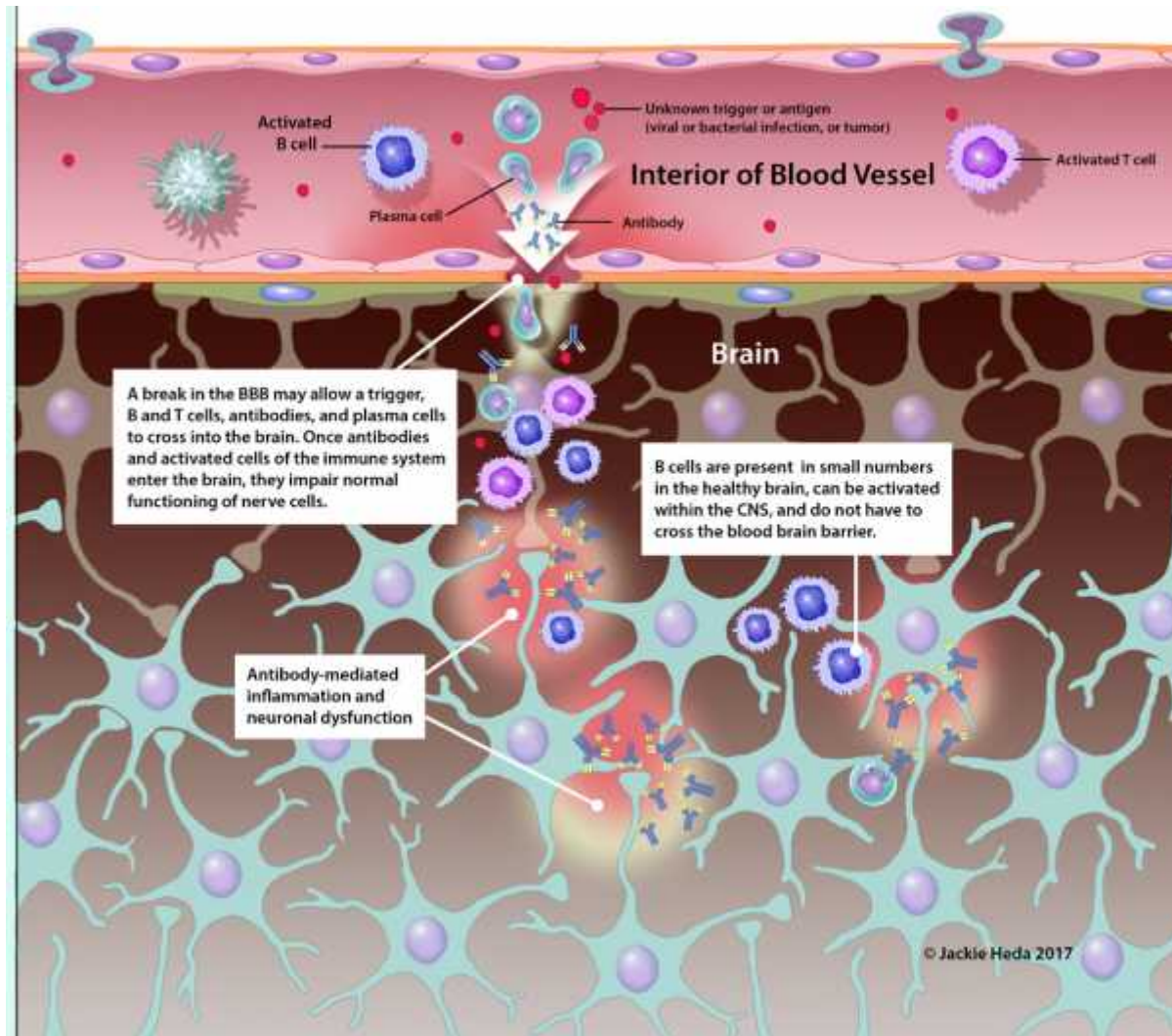
Only specific molecular substances can pass through the BBB: It acts as natural protection for the CNS



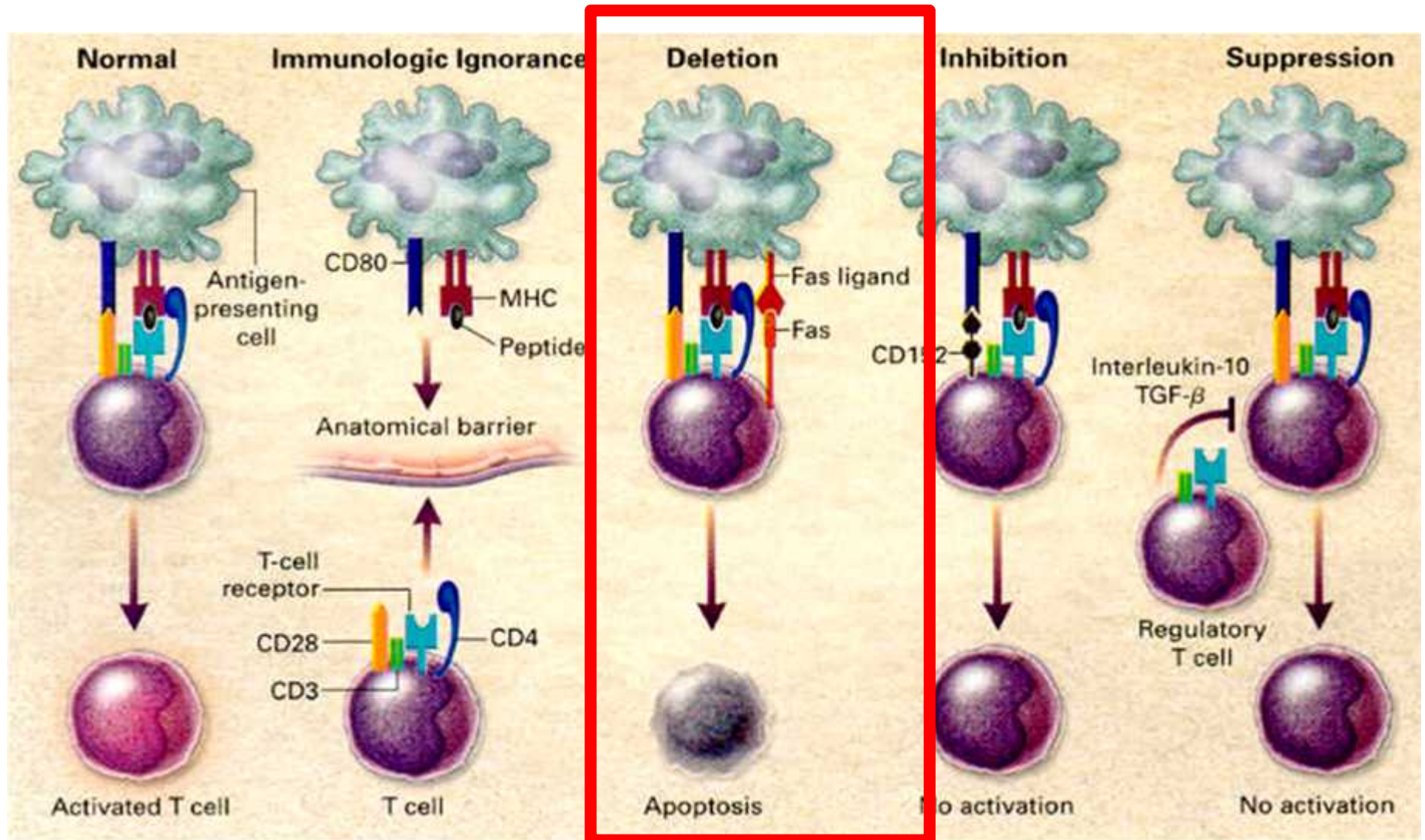
Break of anatomical barriers triggers autoimmunity

The paradigm of multiple sclerosis

Certain infections with bacteria, viruses, fungi, cytokines etc. can trigger break in blood brain barrier, and induce the entrance of inflammatory immune components



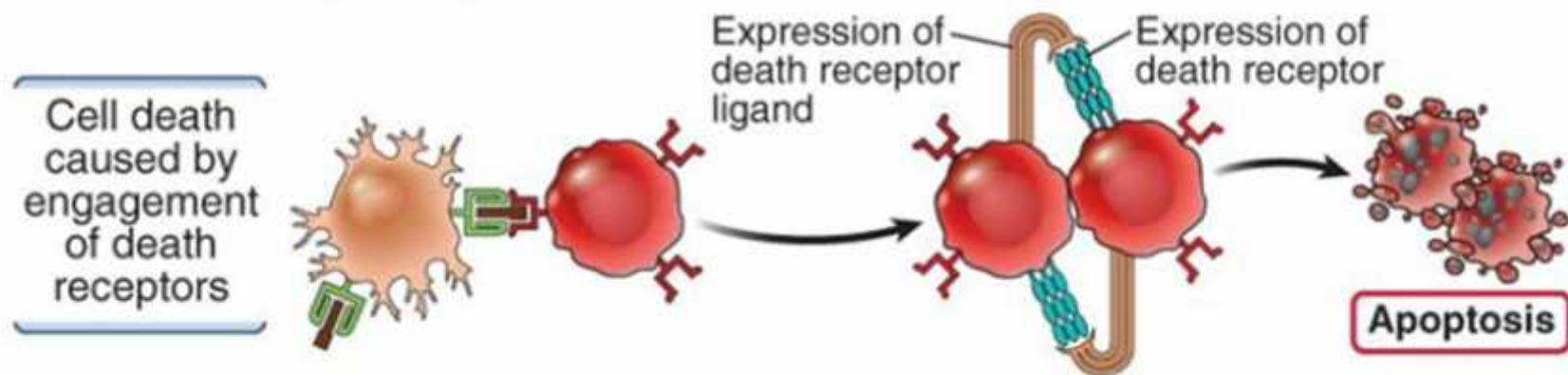
Peripheral mechanisms of tolerance operate to maintain immune homeostasis



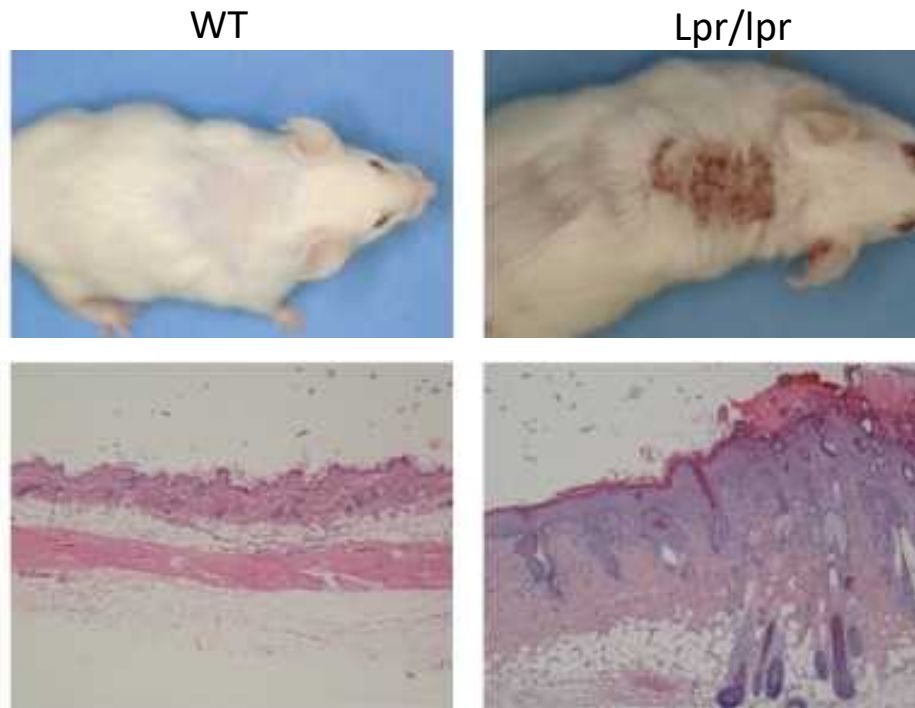
T Cell Peripheral Tolerance: Deletion

- T cells that recognize self antigens without inflammation or that are repeatedly stimulated by antigens die by apoptosis.

2. Repeated stimulation of T cells results in the **coexpression of Fas and FasL**. This interaction results in apoptosis as we've learned before (see L12).

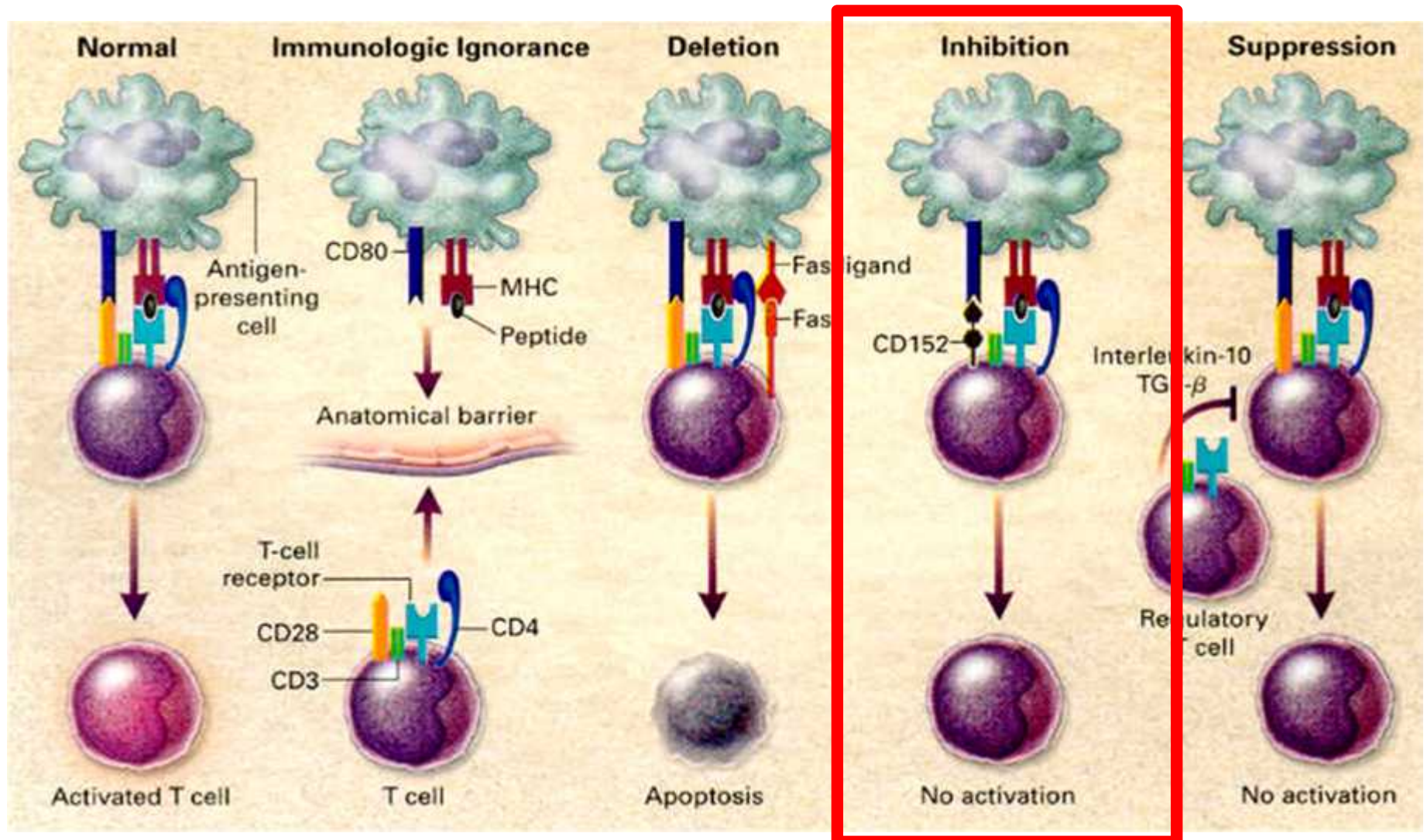


Mutations in the genes encoding Fas/FasL lead to autoimmunity

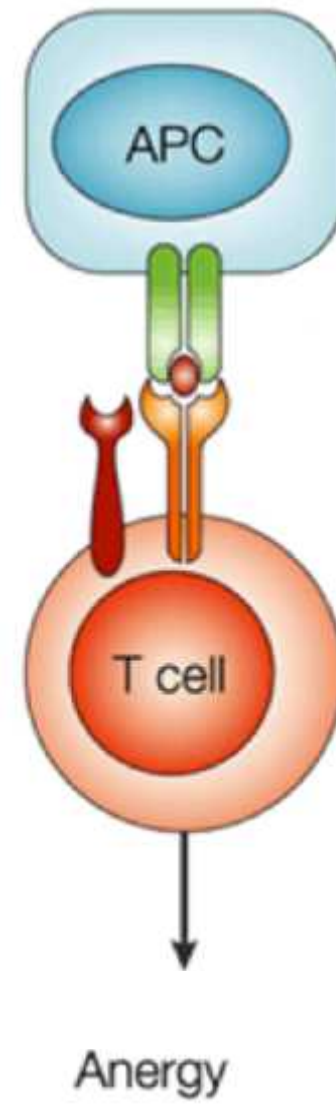
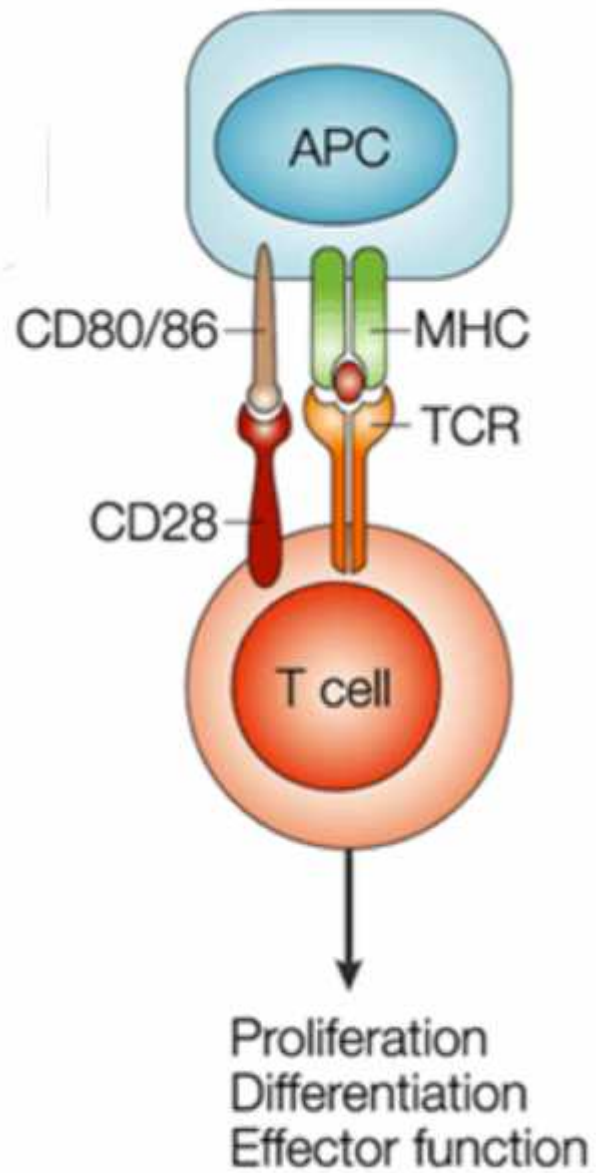


- MRL-*lpr/lpr* mice bear mutations in the gene encoding Fas and serve as a widely used model for autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), and ALPS
- Mice with the *gld/gld* genotype bear mutations in the gene encoding FasL, and they are widely used as a model of autoimmune disease.

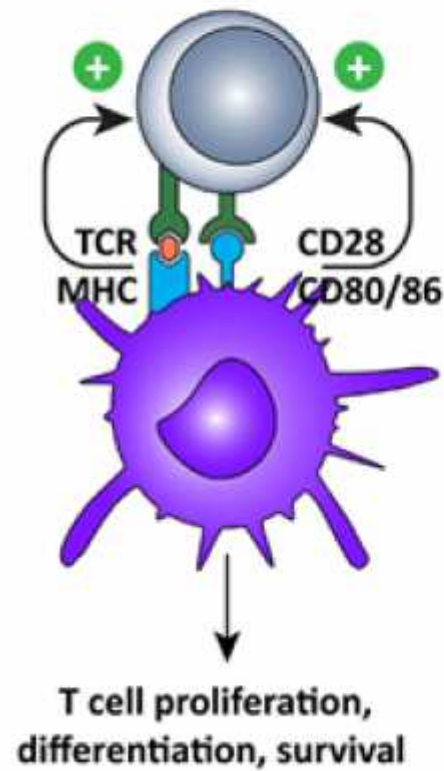
Peripheral mechanisms of tolerance operate to maintain immune homeostasis



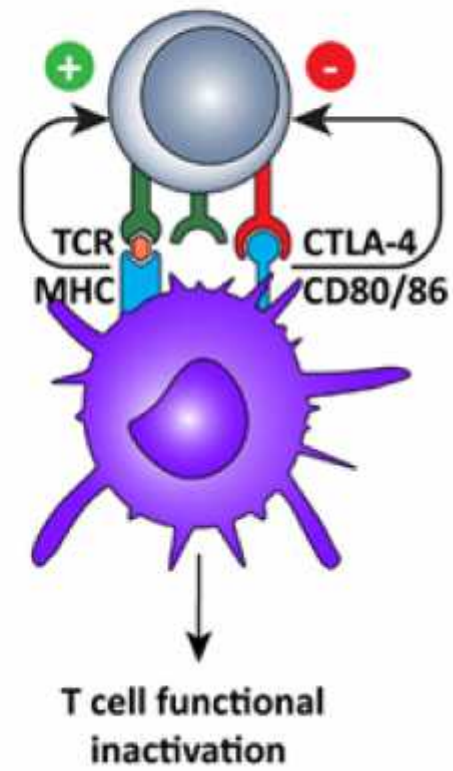
Full activation of T cells requires two signals



T cell Activation



T cell Inhibition

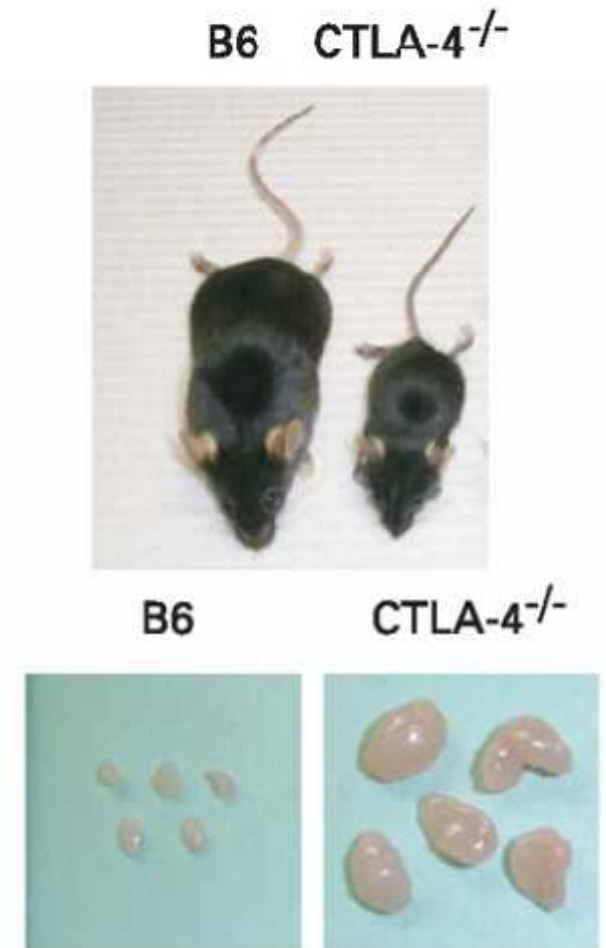


Clinical Application: Defects in CTLA4

Mutations in CTLA4 result in the development of autoimmune responses

- Mice lacking CTLA4 develop uncontrolled lymphocyte activation with massively enlarged lymph tissues and fatal multiorgan lymphocytic infiltrates, suggestive of systemic autoimmunity

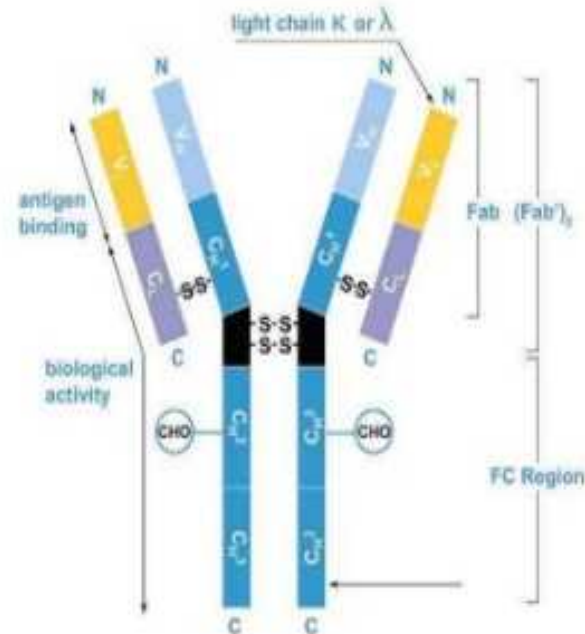
- Polymorphisms in the CTLA4 gene are associated with several autoimmune diseases in humans, including type1 diabetes, SLE, RA and Grave diseases



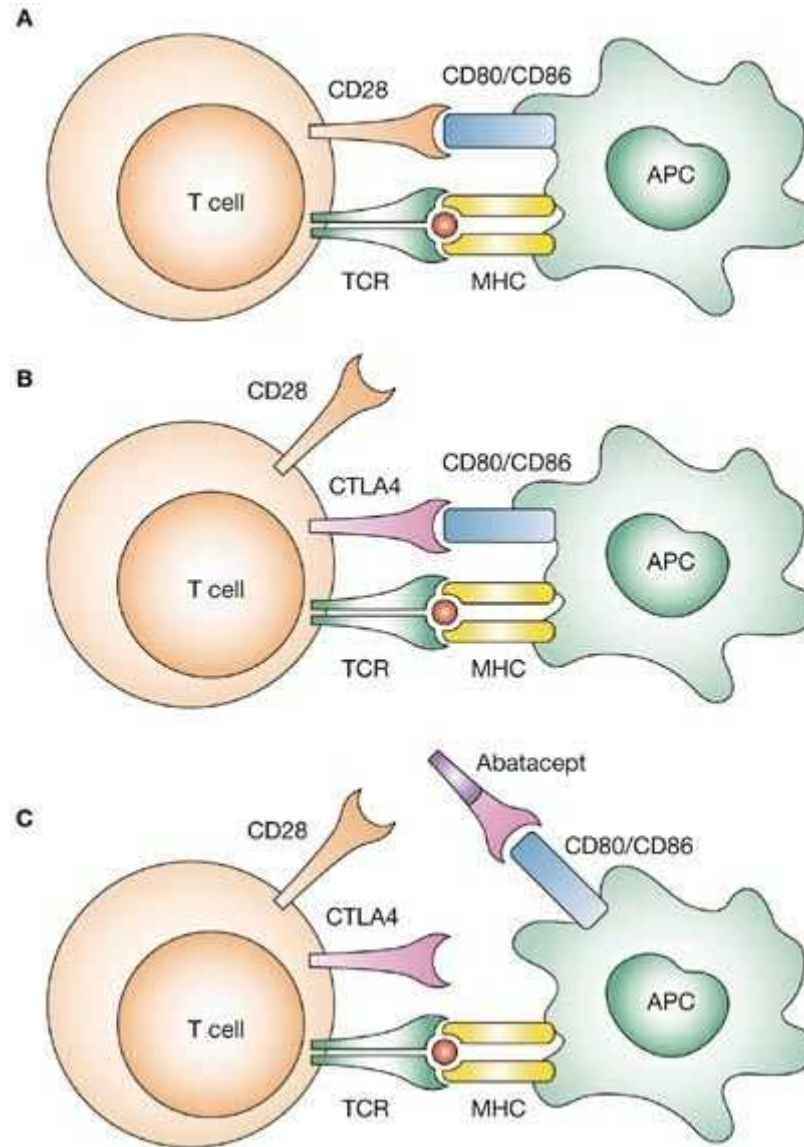
Clinical Application: Therapy based on CTLA4

Orencia (Abatacept)

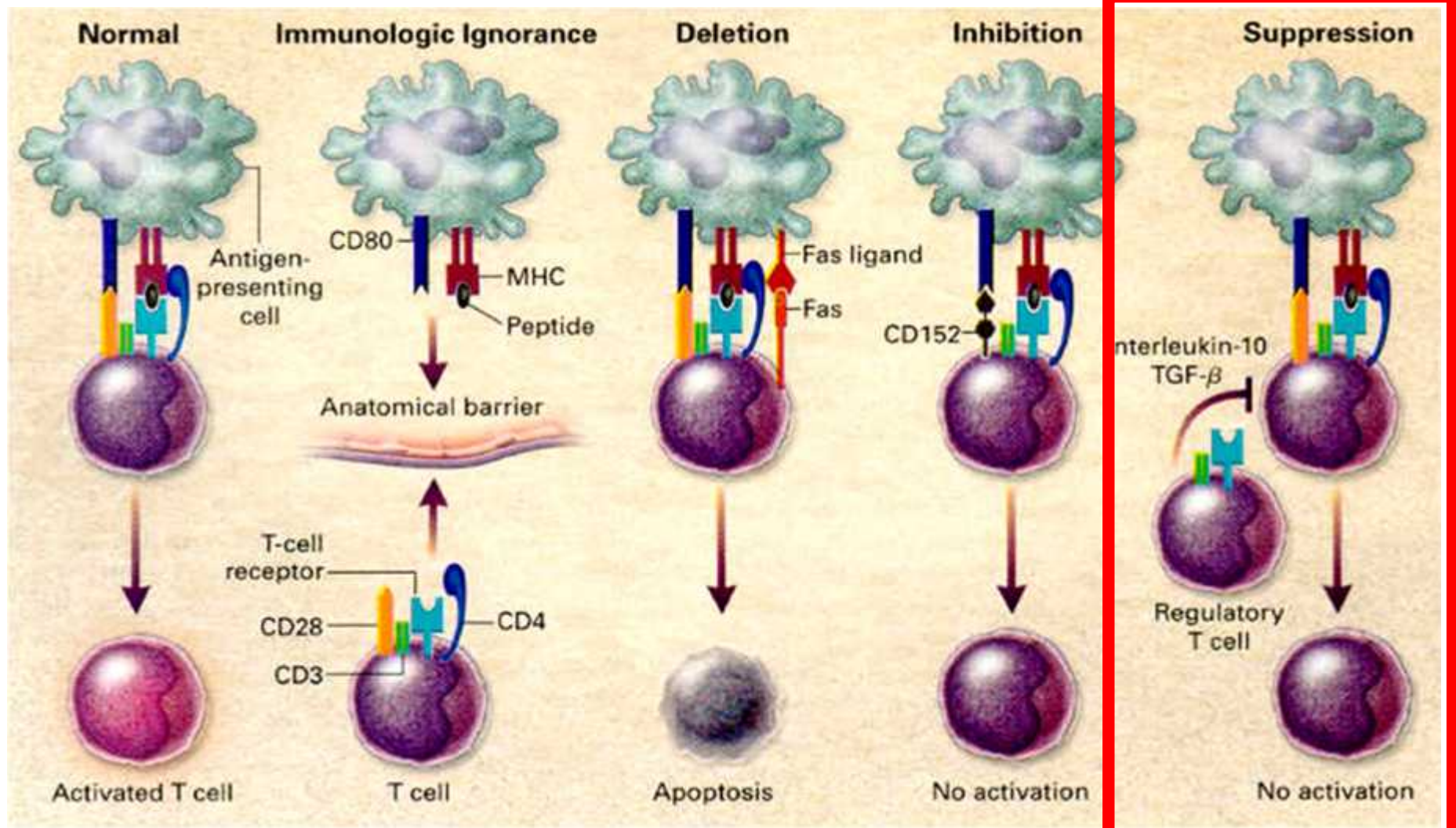
- is a soluble fusion protein that consists of :
 1. the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).
 2. linked to the modified Fc portion of human immunoglobulin G1 (IgG1).



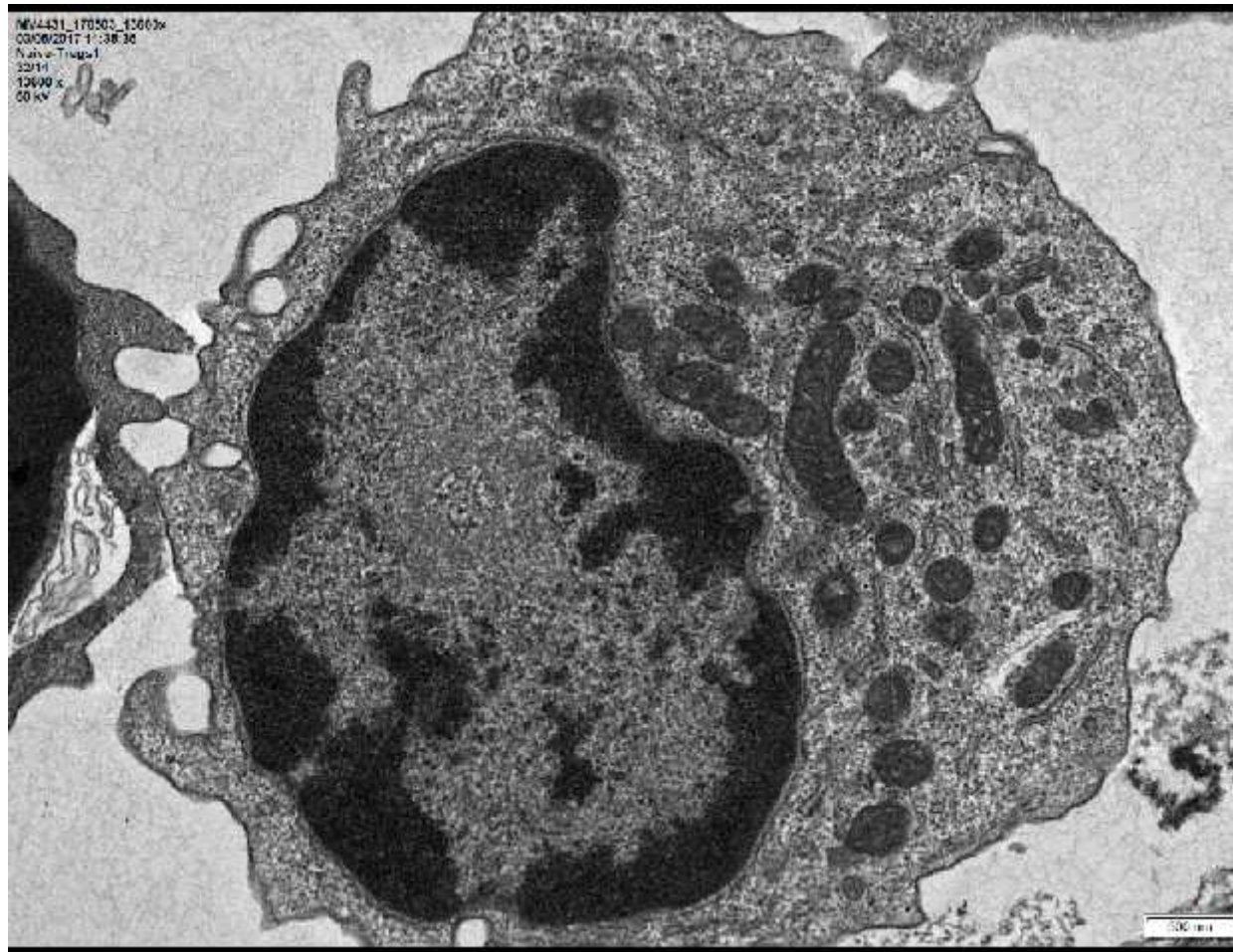
Mechanism of abatacept function



Peripheral mechanisms of tolerance operate to maintain immune homeostasis



Regulatory T cells (Tregs): a dominant mechanism of immune tolerance



Foxp3 an exclusive transcription factor of the Treg cell lineage

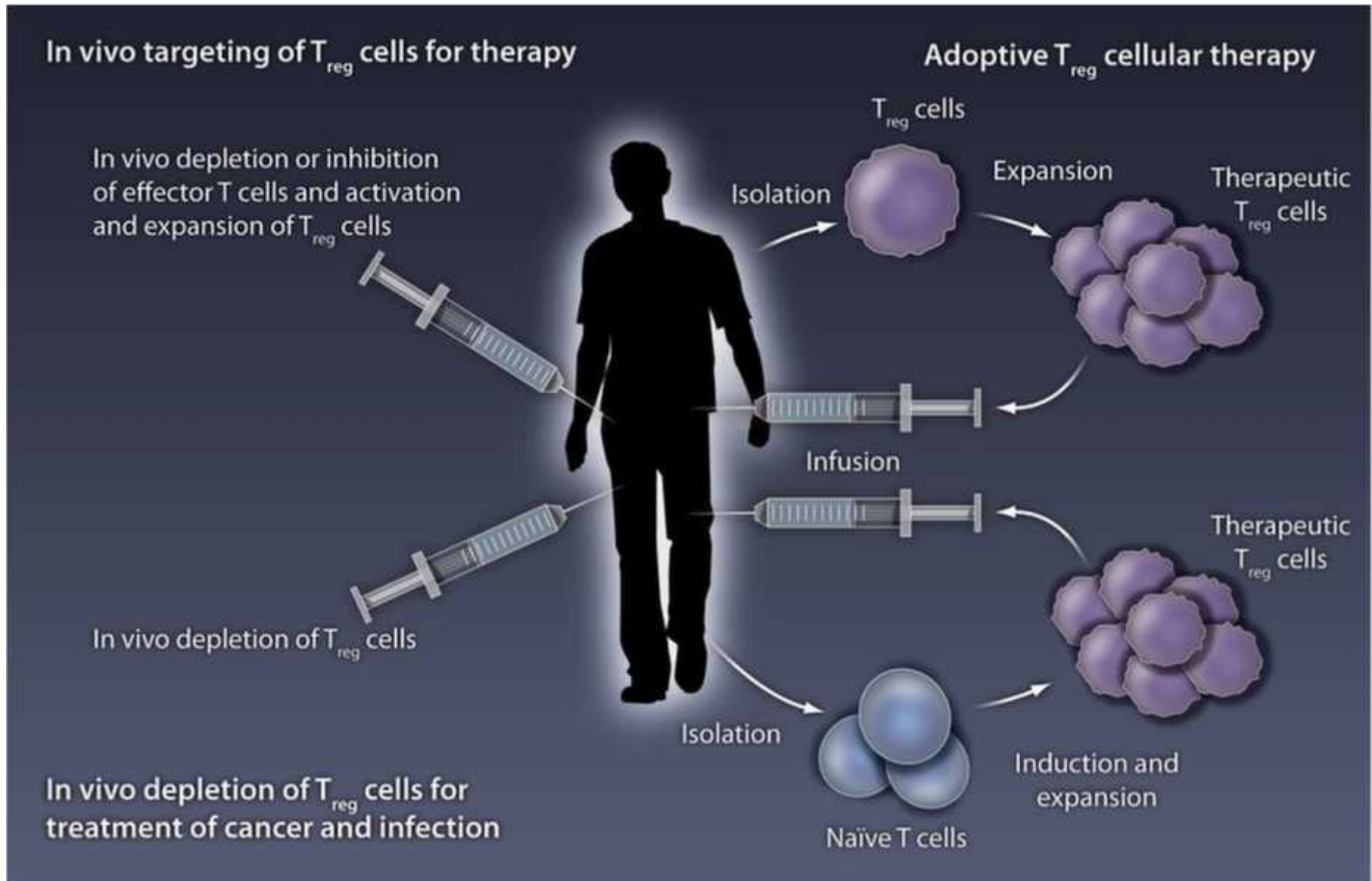
Immunodysregulation Polyendocrinopathy Enteropathy X-linked syndrome (IPEX)

Treg deficiency due to Foxp3 mutation



- Neonatal onset diabetes mellitus
- Hypothyroidism
- Enteritis (diarrhea/villous atrophy)
- Hemolytic anemia & thrombocytopenia.
- Dermatitis
- Dermatitis (eczema)
- Death by 1-2 years of age

Treg cell immunotherapy



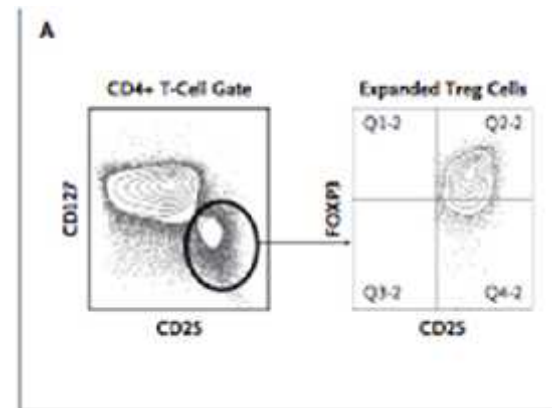
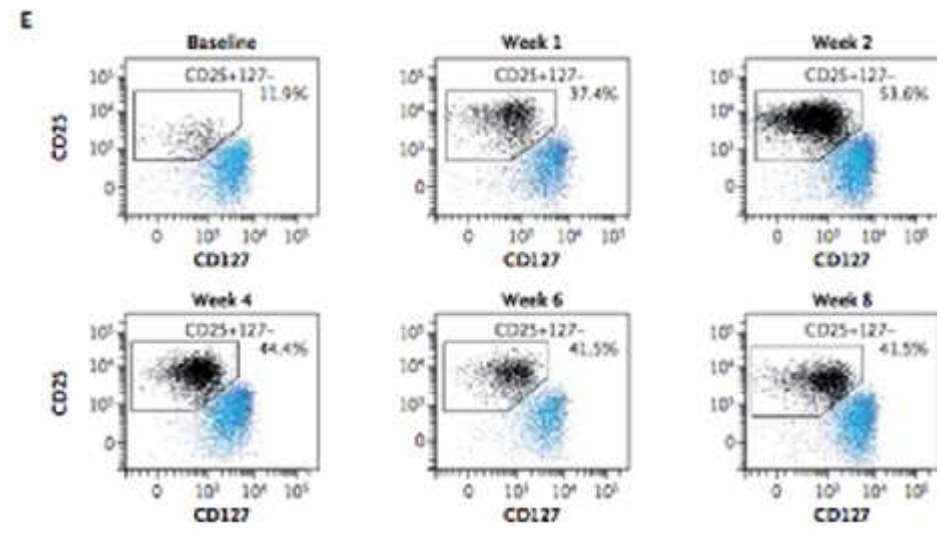
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

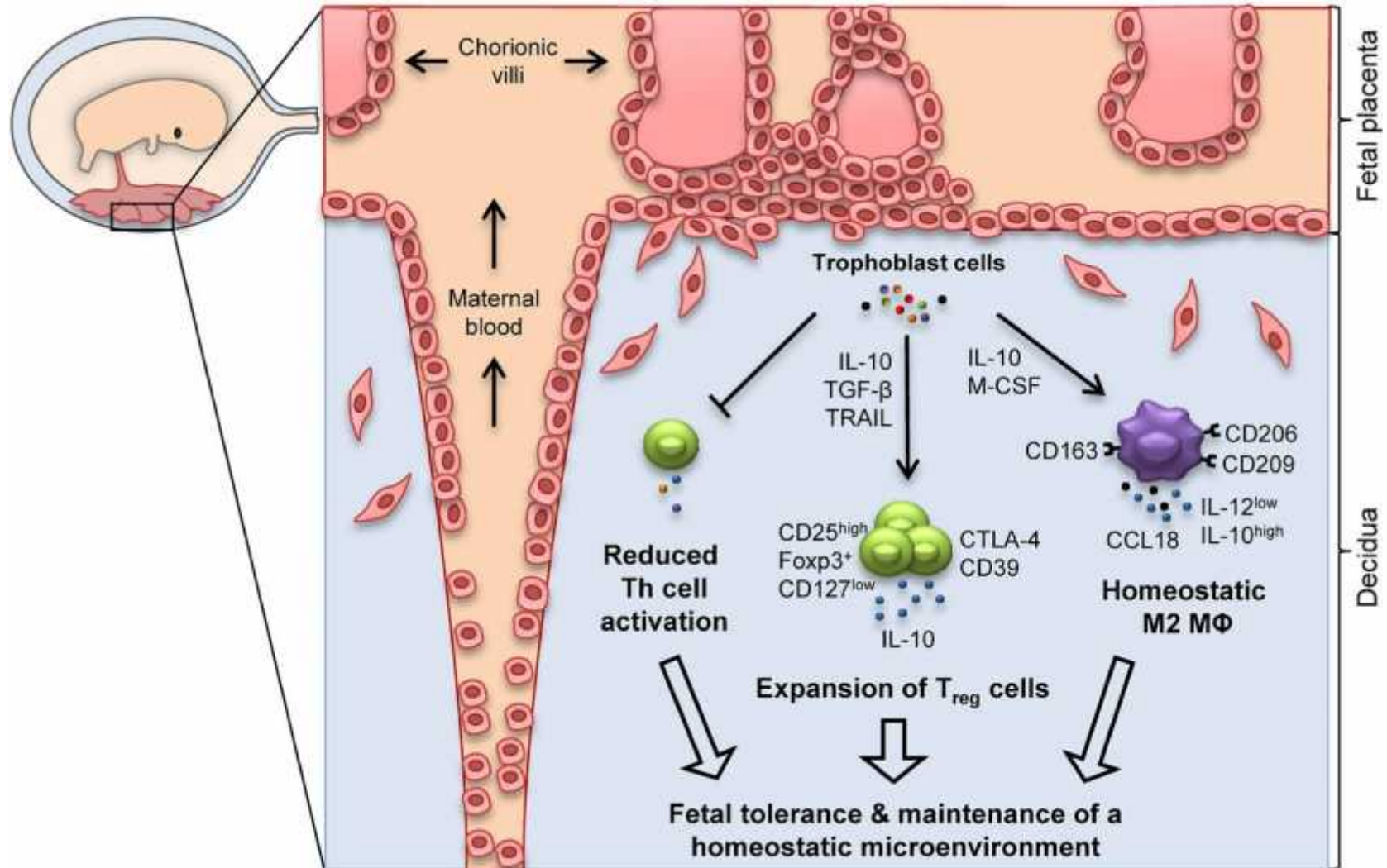
DECEMBER 1, 2011

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Interleukin-2 and Regulatory T Cells in Graft-versus-Host Disease



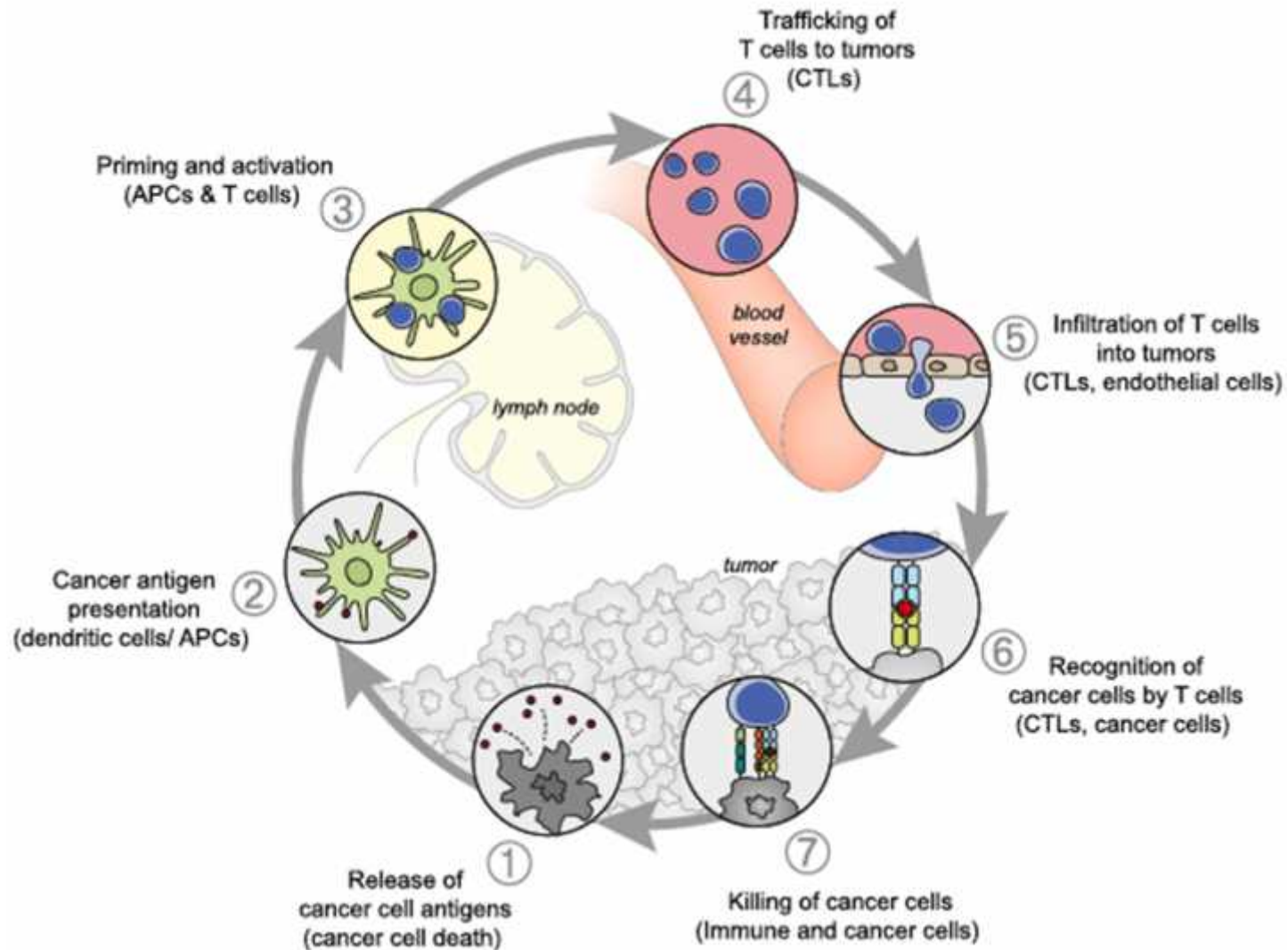
Fetal Tolerance



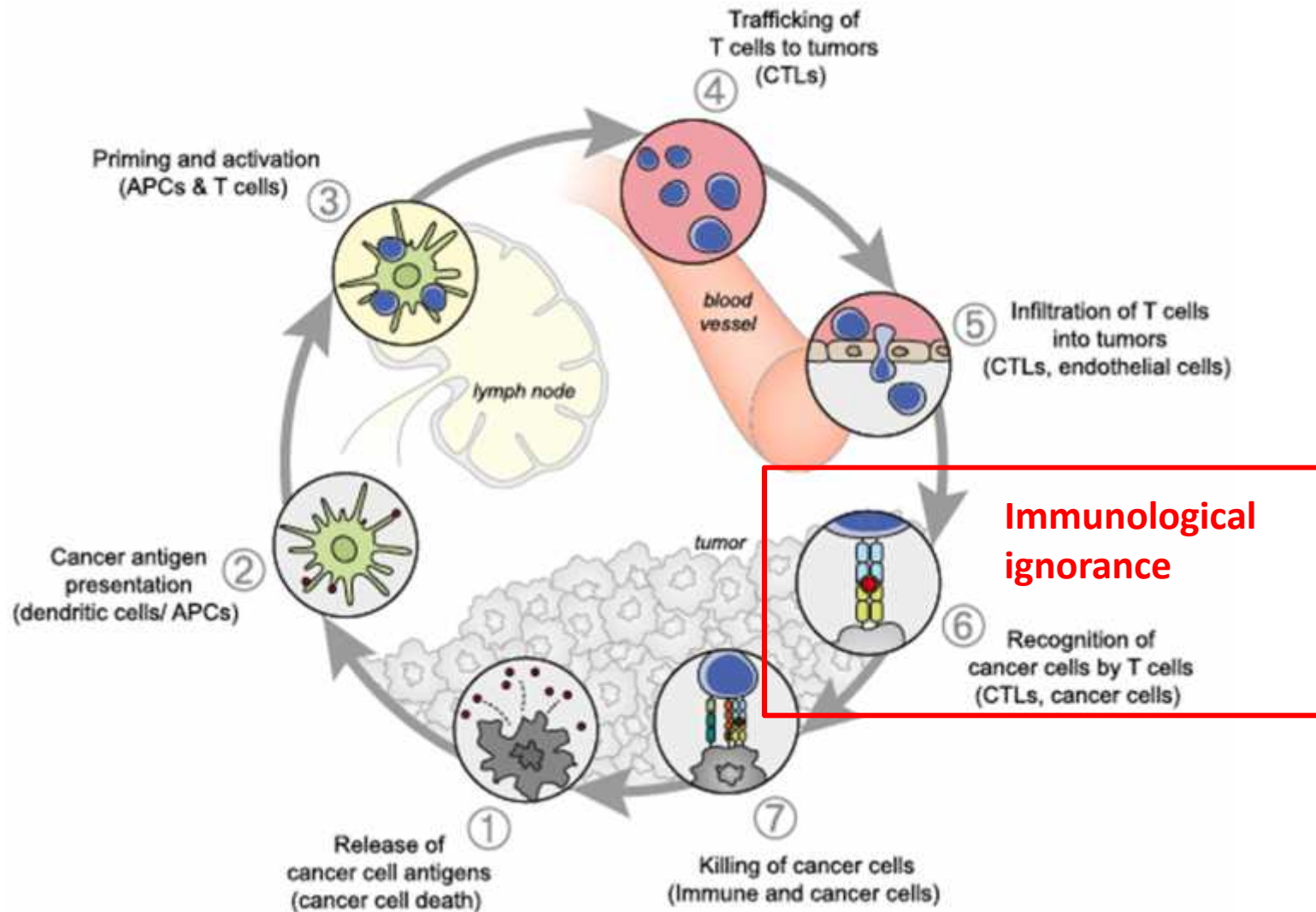
Is tolerance good?



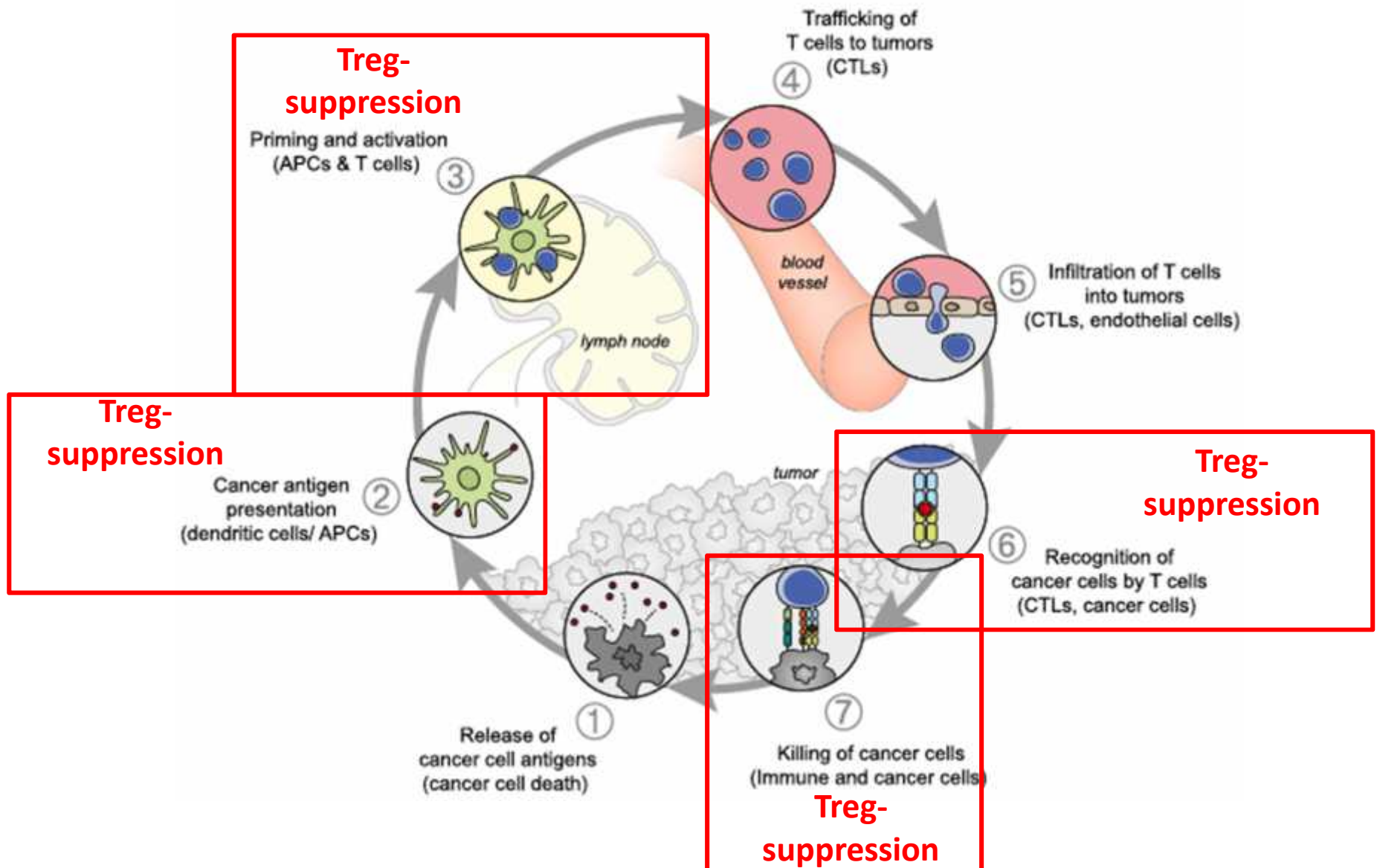
The optimal anti-tumor immune response without tolerogenic mechanisms



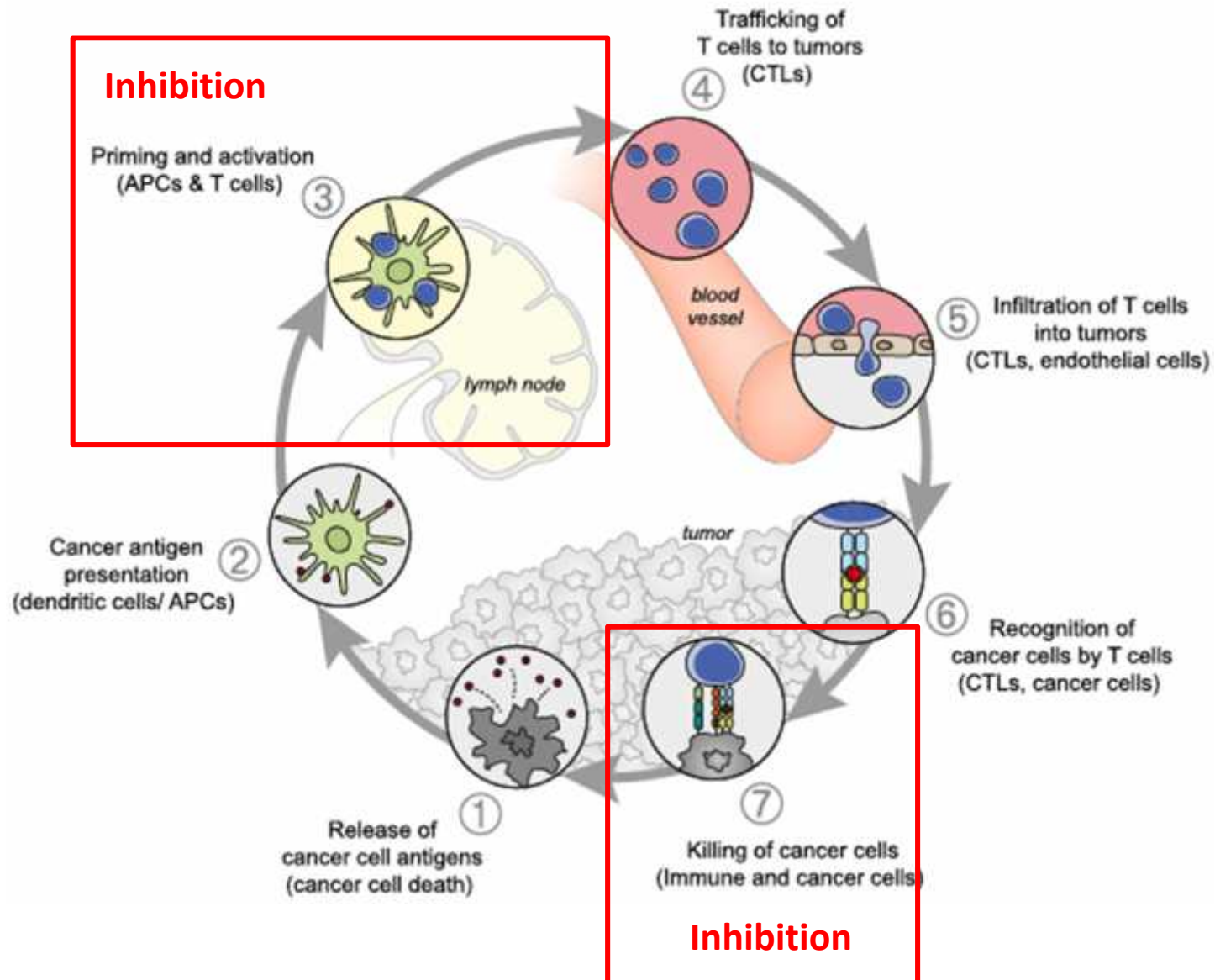
Immunological ignorance in cancer



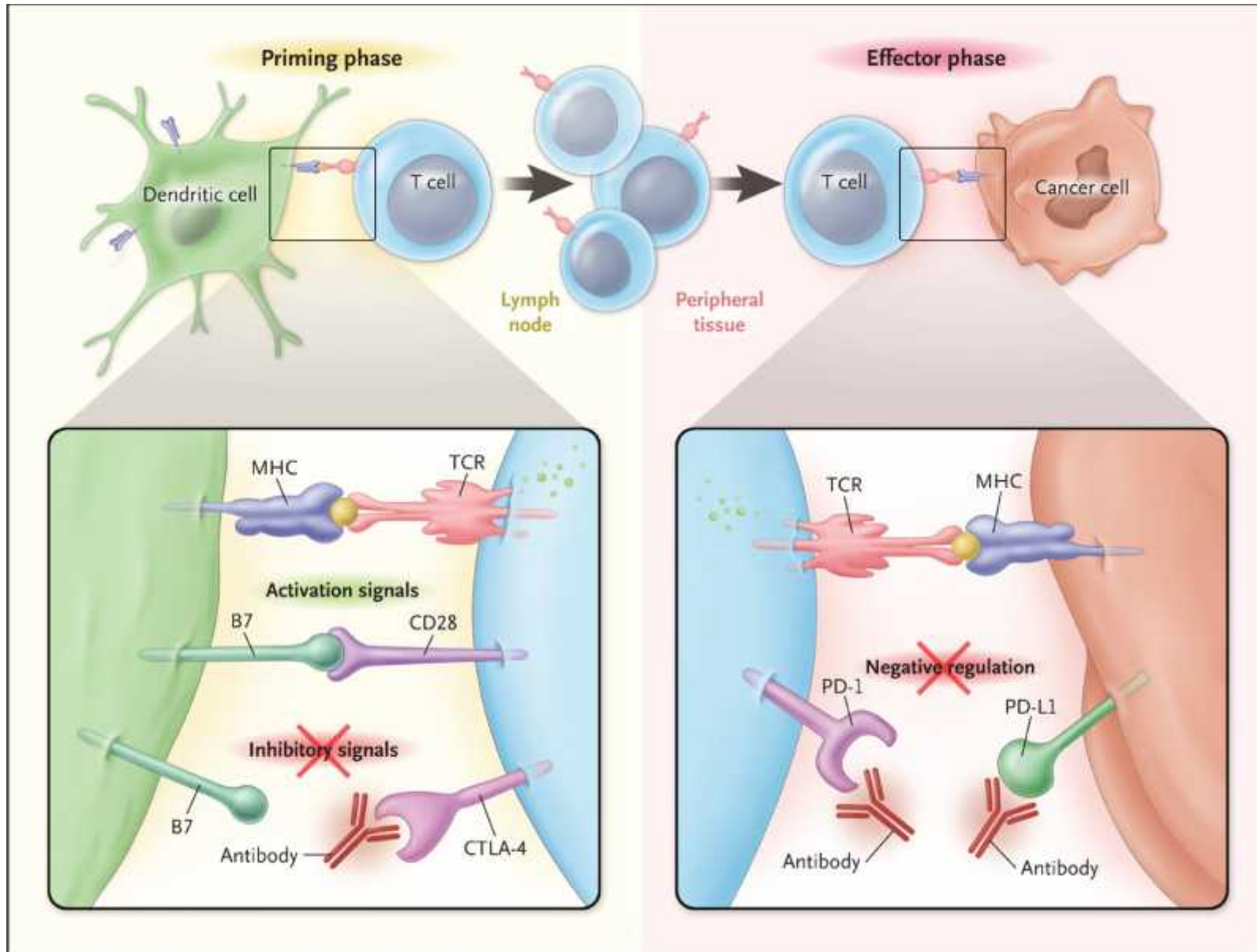
Treg-suppression in cancer



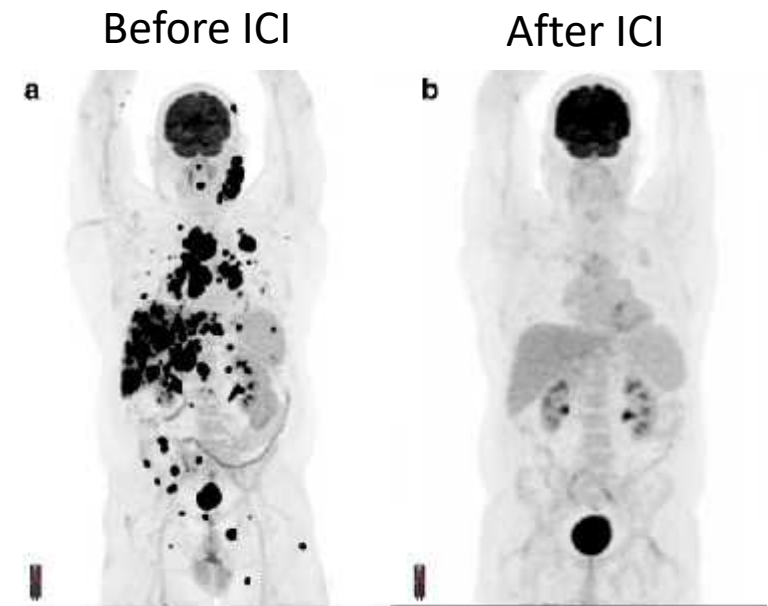
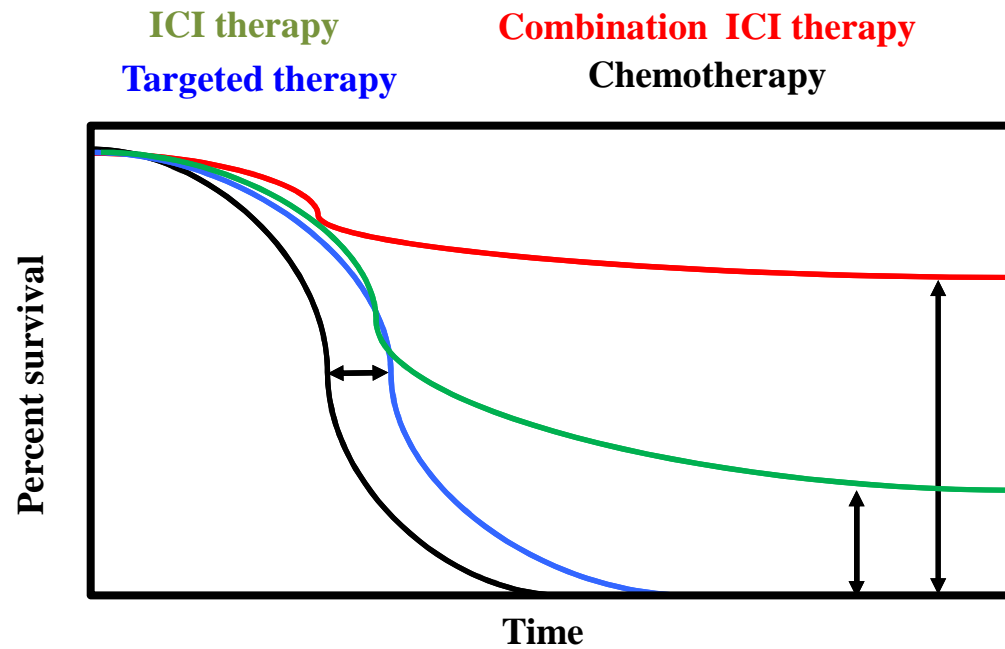
Immunological inhibition in cancer



Immune checkpoint inhibitors (ICI): a paradigm shift in cancer immunotherapy



Increased survival of patients with advance malignancies upon ICI immunotherapy



THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2018

Illustrations: Niklas Elmehed

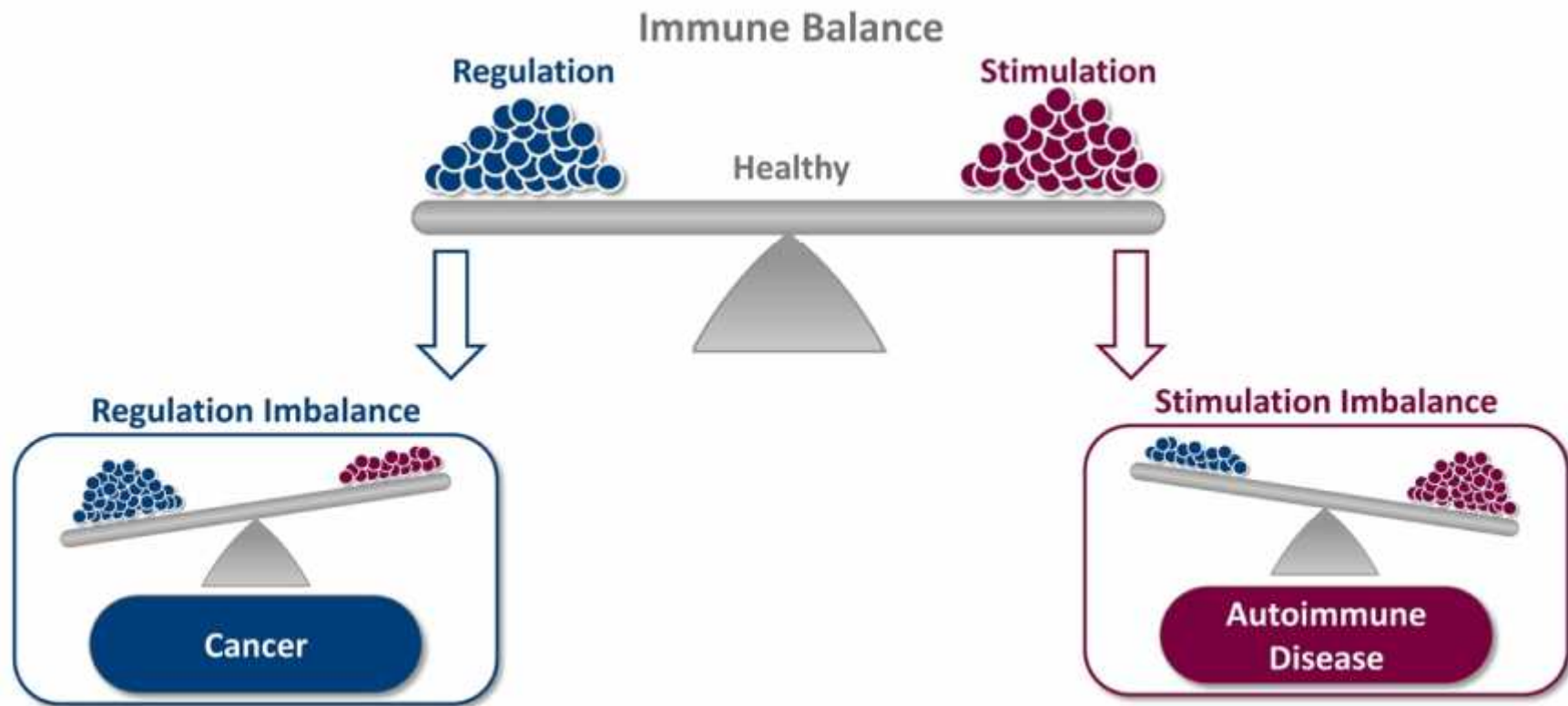


James P. Allison • Tasuku Honjo

“for their discovery of cancer therapy by inhibition
of negative immune regulation”


THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

Unbalance of immune tolerance in Autoimmunity and Cancer

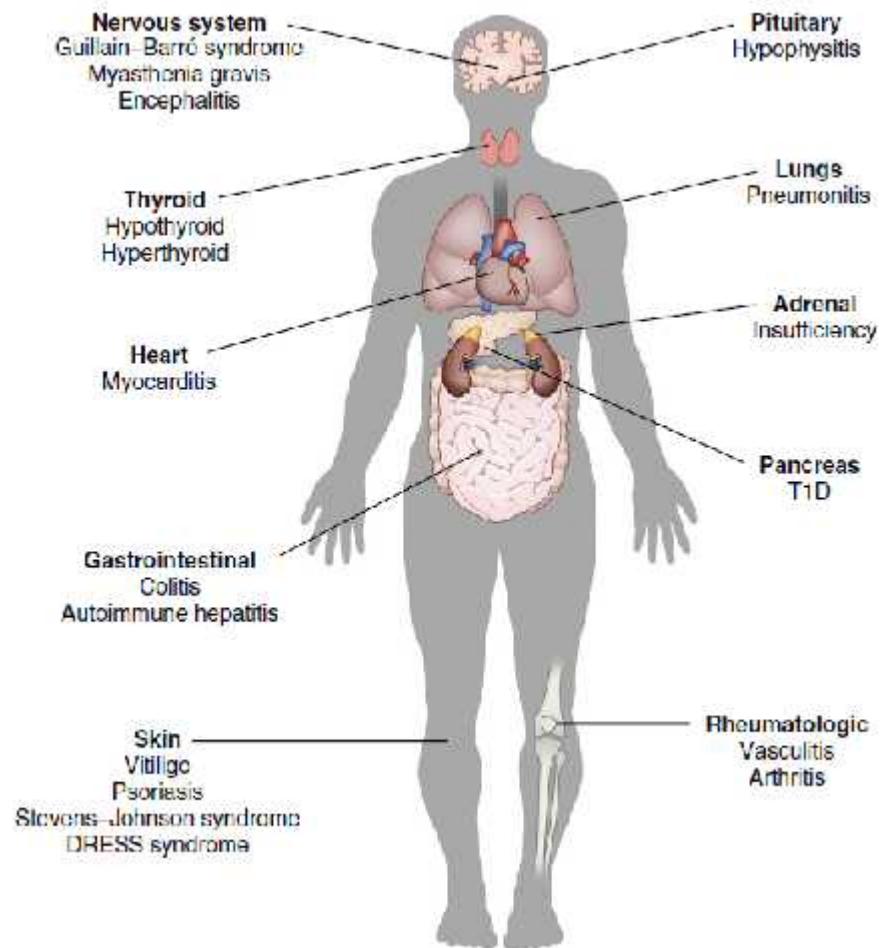


Challenges and pitfalls

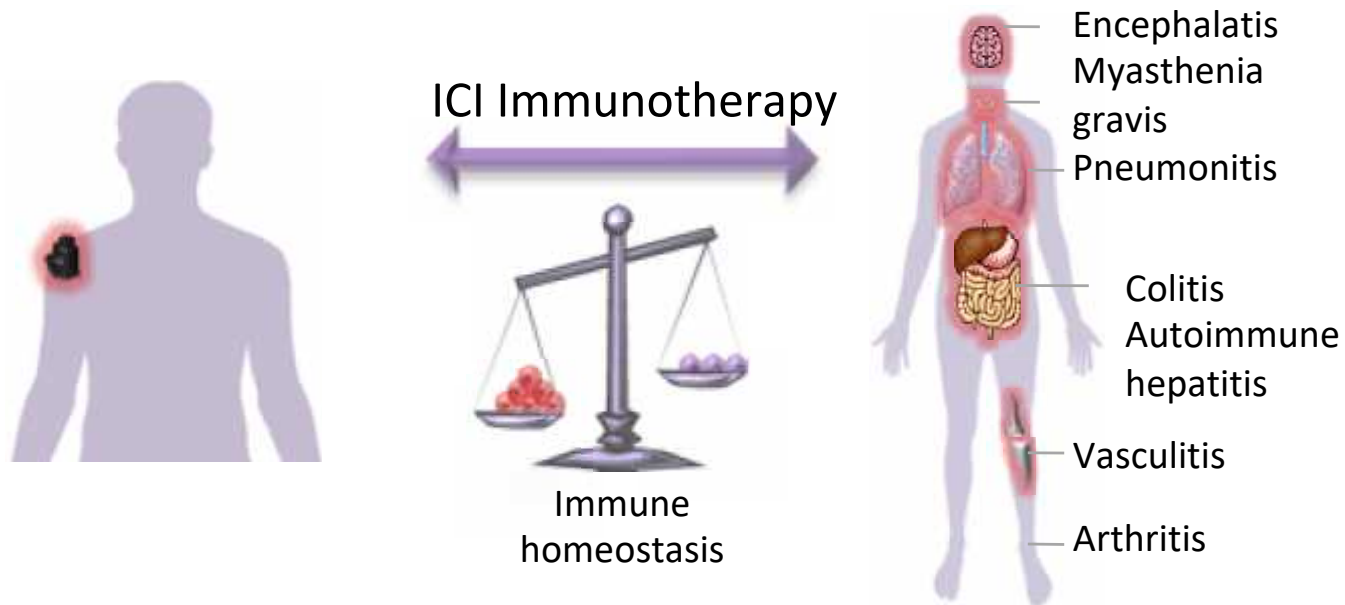
Is autoimmunity the Achilles' heel of cancer immunotherapy?

Carl H June^{1,2} , Jeremy T Warshauer³ & Jeffrey A Bluestone^{1,4}

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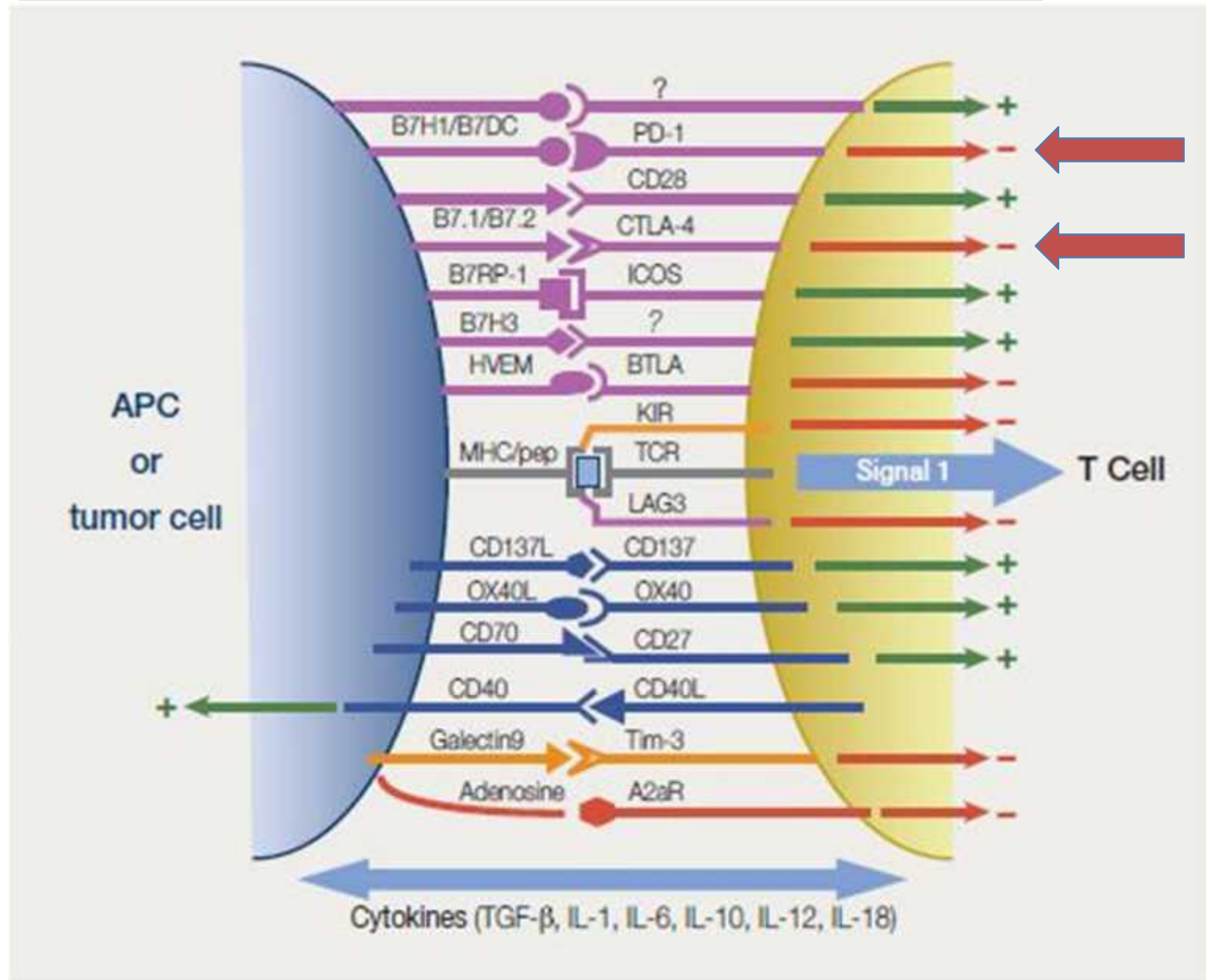
Immunotherapy shifts the tolerance balance towards autoimmunity



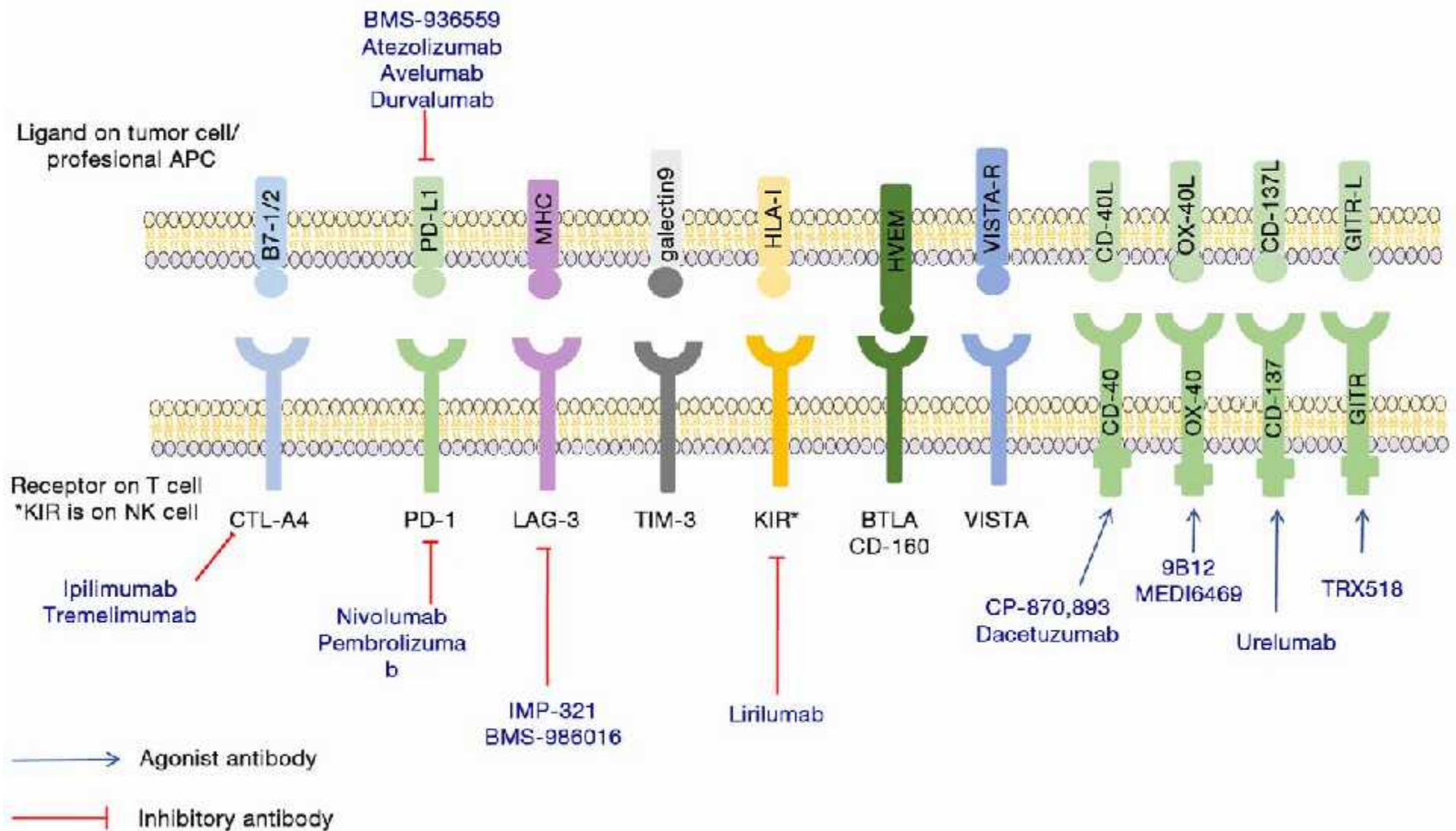
Alissafi T. et al *J. Autoimmun.* 2019

Immunological inhibition in cancer

Co-stimulatory and co-inhibitory receptors (Immune checkpoints)



The more Checkpoint Blocking/Agonist Antibodies the more IrAEs?



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