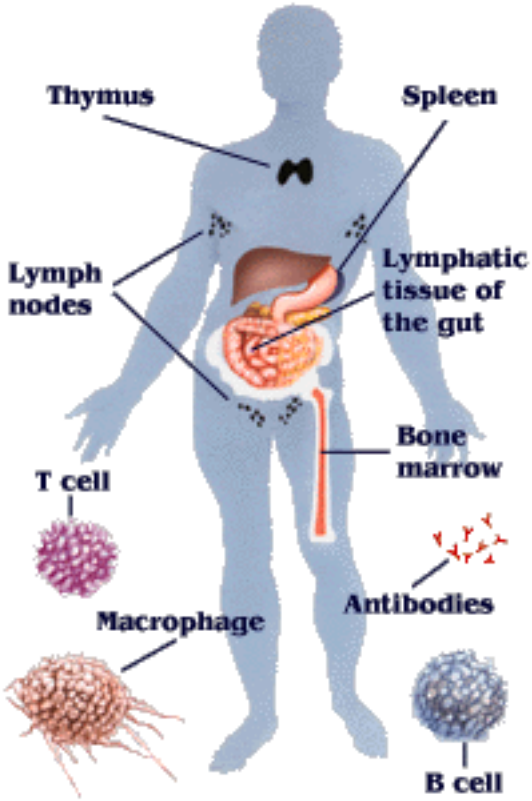
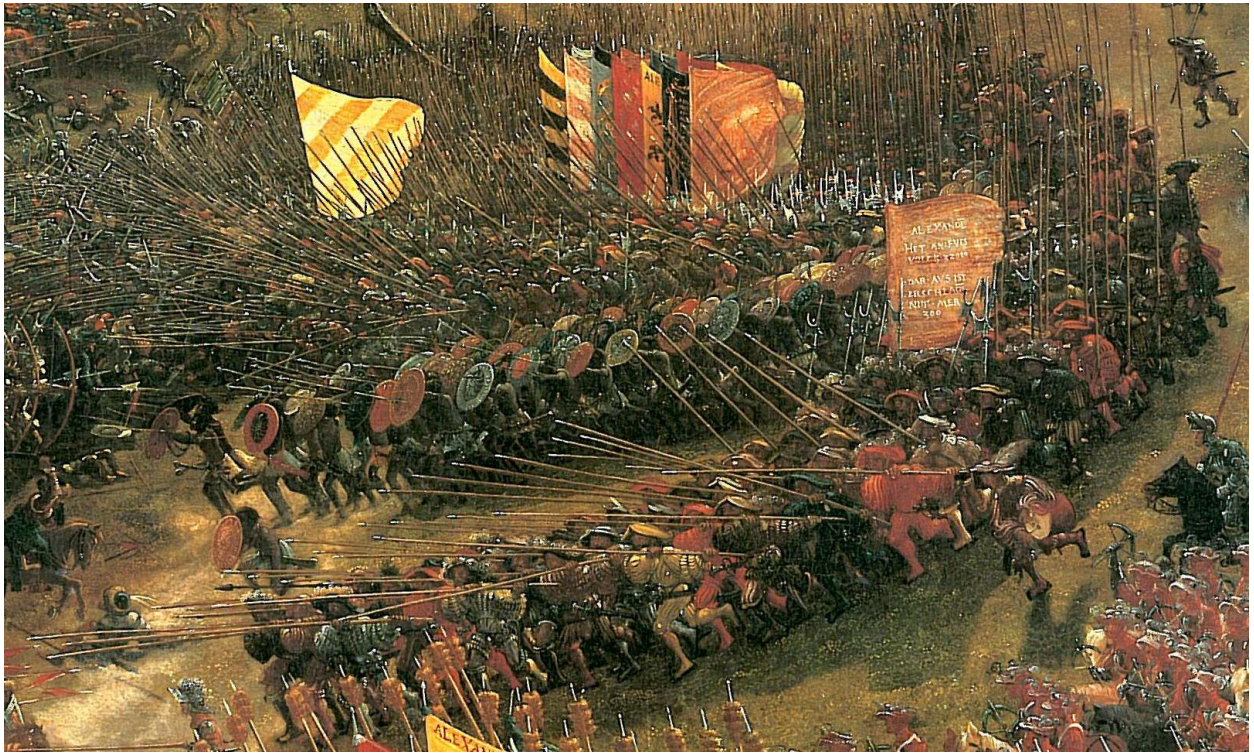
Manipulation of the Immune Response - Immunomodulation -

Janeway's Immunobiology, 9th ed., 2017.

Immune system

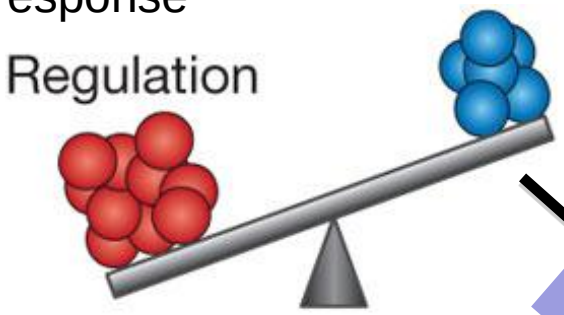




Immune system is made of components, cells and organs that act together to defend the host from microbes.

Aim of immunomodulation

Hyperimmune response

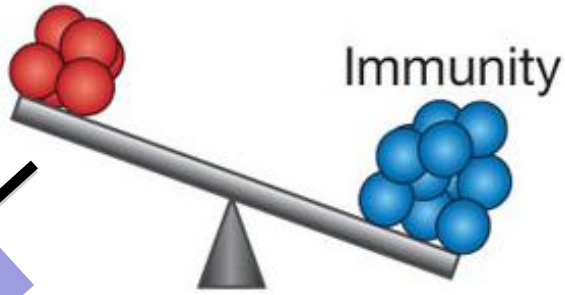


E.g.
- Autoimmune diseases
- Allergies
- Transplant rejection

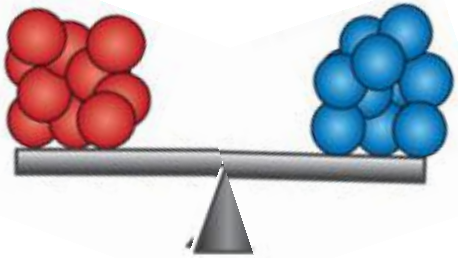
tolerance

response

Hypoimmune response



E.g.
- Infections
- carcinomas



Immunomodulation methods

IMMUNOSUPPRESSION:

- Immunosupressive drugs
- Monoclonal antibodies
- Gene manipulation (CRISPR-Cas9, siRNA)

IMMUNOSTIMULATION:

- Antitumor therapy
- BCG, adjuvans
- Interferons
- Talidomide, levamisol
- IL-2

- IMMUNISATION

- Vaccination
- Immunoglobulins

Immunosupression

When?

- Autoimmune diseases
- Organ transplantation
- Allergies

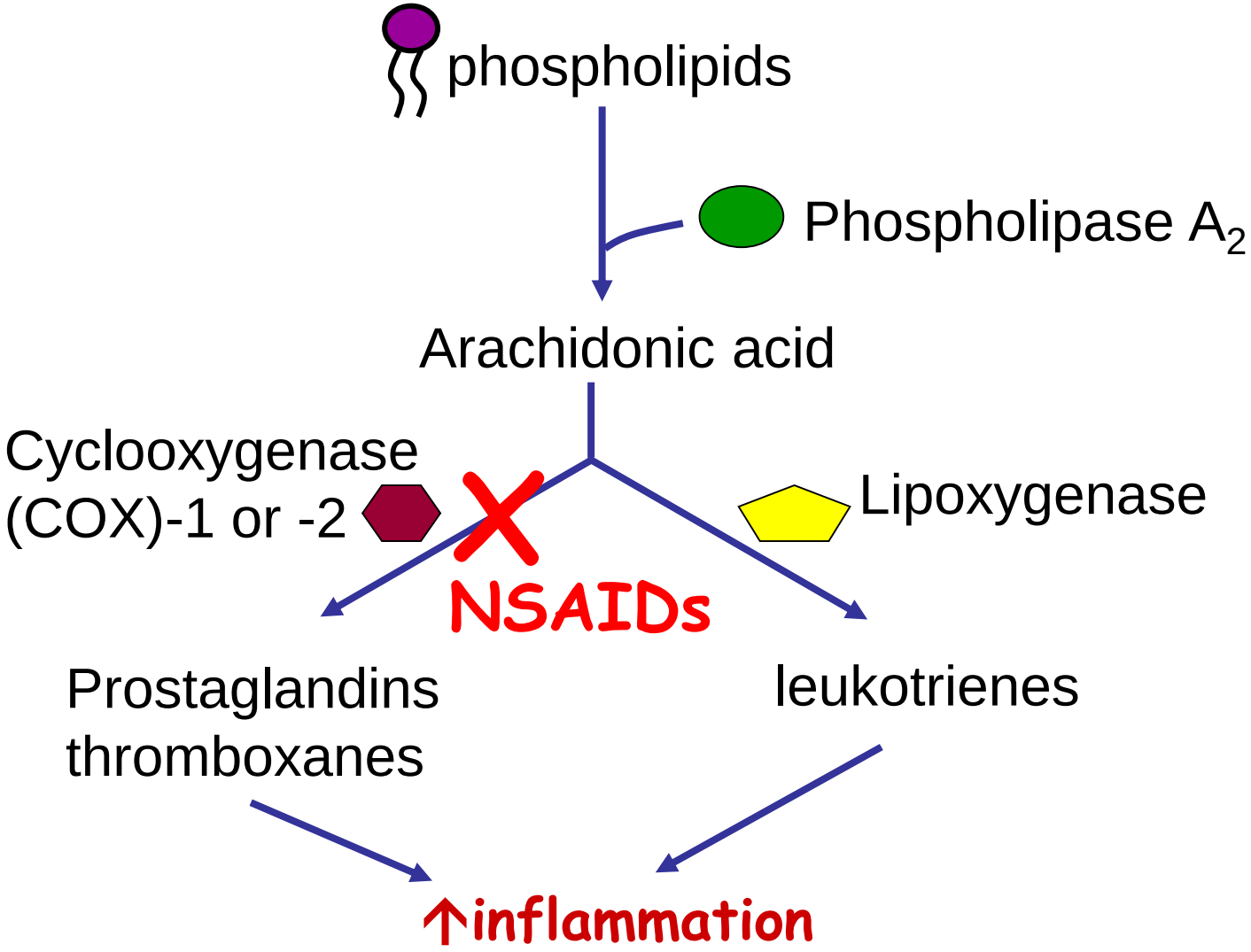
Problems:

- Lifetime usage of drugs
- Infections, tumors
- Nephrotoxicity
- Diabetogenic

Immunosupressive drugs

- Anti-inflammatory (NSAIDs, corticosteroids)
- Cytotoxic (azathioprine, cyclophosphamide)
- Noncytotoxic (cyclosporin A, tacrolimus, rapamycin)

Immunosuppressive drugs: Nonsteroid anti-inflammatory drugs - NSAIDs



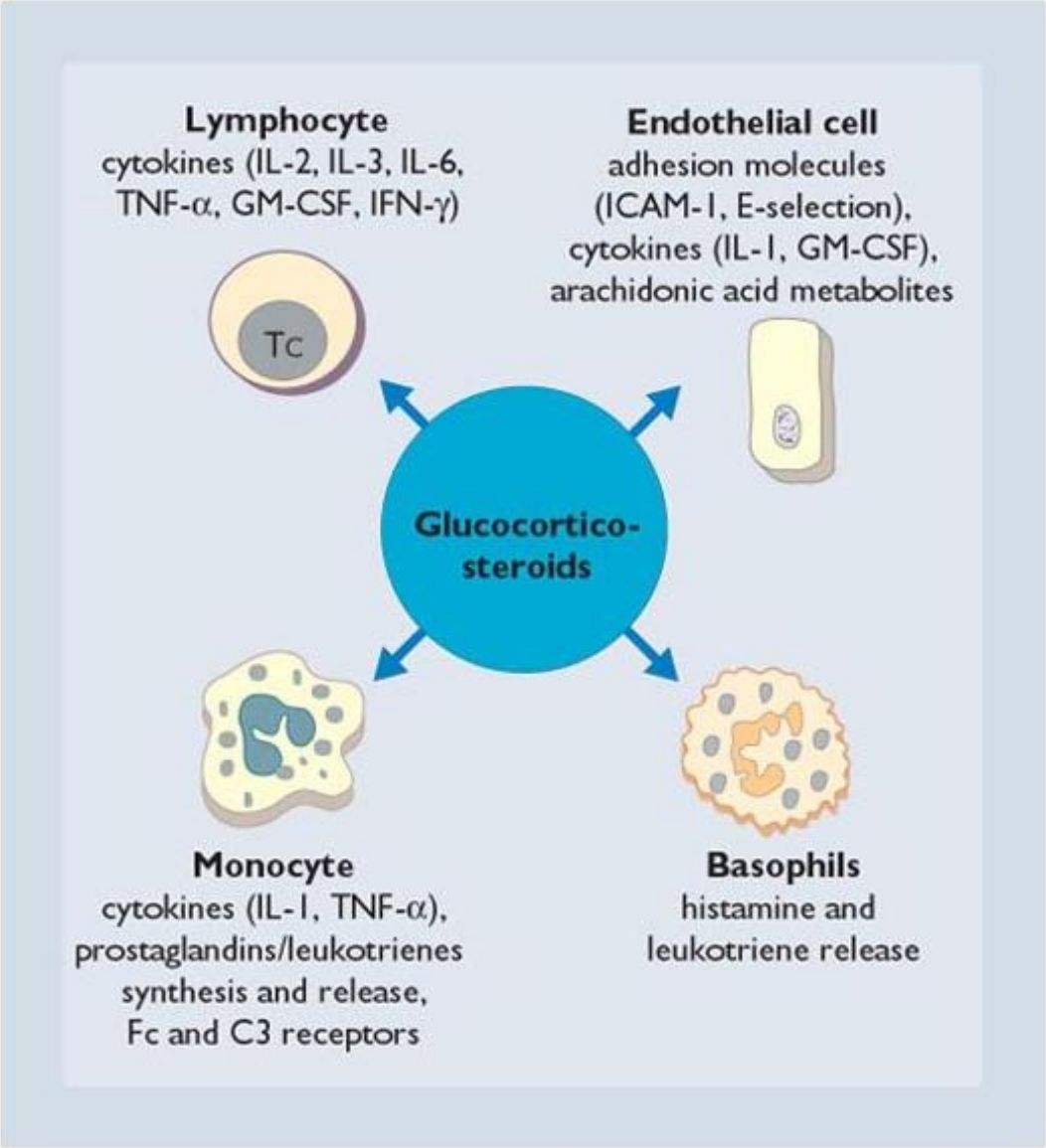
Immunosuppressive drugs: steroids

- **Corticosteroids** = powerfull anti-inflammatory drugs
  - **Prednisone** (synthetic cortisol analog)
  - Used in transplantations, autoimmune diseases, allergies
  - Activated steroid receptors act as transcription factors

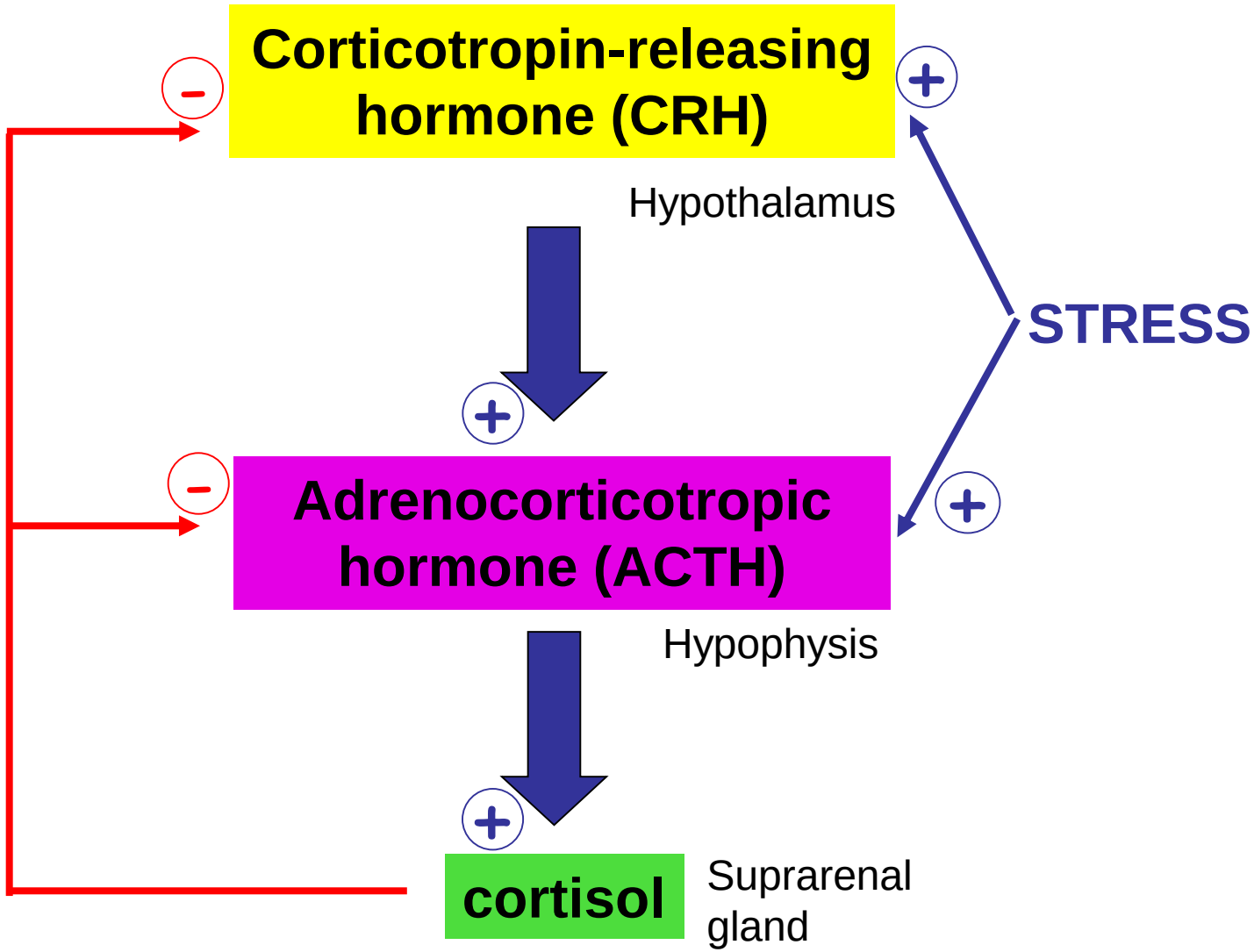
Corticosteroid therapy	
Effect on	**Physiological effects**
↓ IL-1, TNF-α, GM-CSF ↓ IL-3, IL-4, IL-5, CXCL8	↓ Inflammation caused by cytokines
↓ NOS	↓ NO
↓ Phospholipase A_2 ↓ Cyclooxygenase type 2 ↑ Annexin-1	↓ Prostaglandins ↓ Leukotrienes
↓ Adhesion molecules	Reduced emigration of leukocytes from vessels
↑ Endonucleases	Induction of apoptosis in lymphocytes and eosinophils

Figure 16.3 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immunosuppressive drugs: steroids

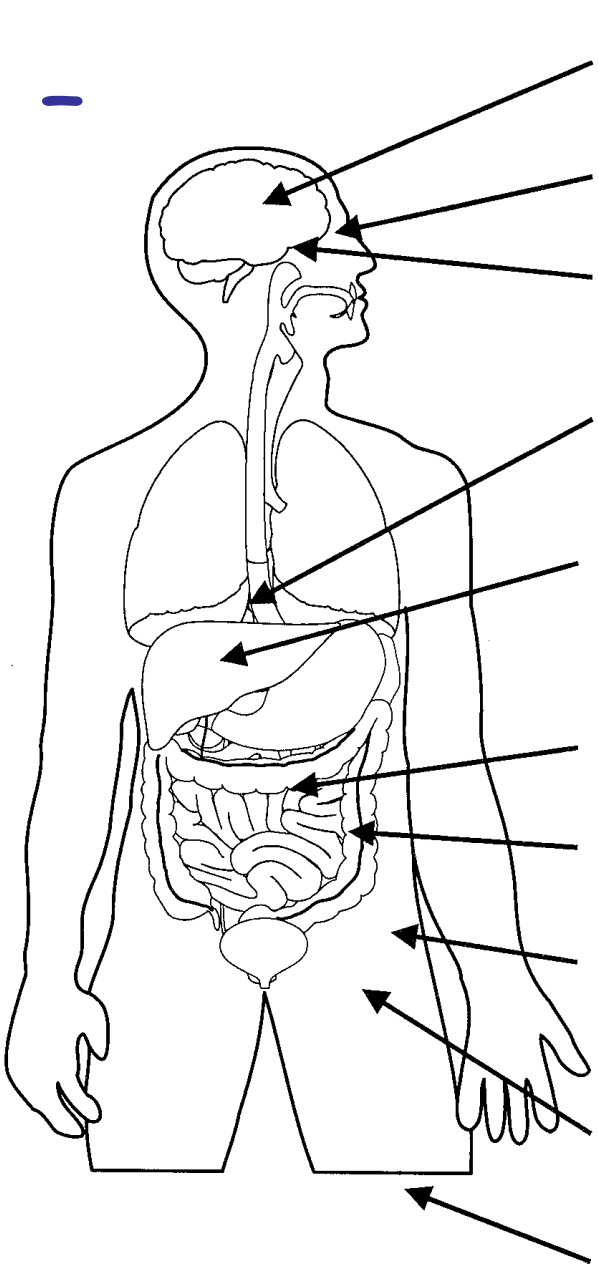


Corticosteroids – physiology



Corticosteroids – physiology

- Possible multiple side effects
- Used in combination with other drugs to reduce toxicity



Brain/CNS:
Depression
Psychosis

Eye:
Glaucoma

Endocrine system:
↓ LH, FSH release
↓ TSH release
↓ GH secretion

GI tract:
Peptic ulcerations

Carbohydrate/lipid metabolism:
↑ hepatic glycogen deposition
↑ peripheral insulin resistance
↑ gluconeogenesis
↑ free fatty acid production
Overall diabetogenic effect

Adipose tissue distribution:
Promotes visceral obesity

Cardiovascular/Renal:
Salt and water retention
Hypertension

Skin/muscle/connective tissue:
Protein catabolism/collagen breakdown
Skin thinning
Muscular atrophy

Bone and calcium metabolism:
↓ bone formation
↓ bone mass and osteoporosis

Growth and Development:
↓ linear growth

Immune system:
Anti-inflammatory action
Immunosuppression

from P. Stewart, Williams Textbook of Endocrinology, 2003

Immunosupressive cytostatics

- Azathioprine, cyclophosphamide
  - Interfere with DNA synthesis (dividing cells)
  - Primarily planned to be used for anti-tumor therapy
  - Used in low dosage for autoimmune diseases (combination with corticosteroids)
  - Used in high dosage only before bone marrow transplantation to eliminate all lymphocytes
  - Cyclophosphamide (more toxic) – developed as chemical weapon (*Mustard gas,* 1917.)

Non cytotoxic Immunosupressives

- Cyclosporin A
  - Discovered in 1971. (1976.)
- and Tacrolimus (FK506)
  - Less toxic
  - Bacterial/fungal origin
  - Interfere with clonal expansion of activated lymphocytes
  - Used in transplanted patients
  - Block calcineurin (cyclosporin A & tacrolimus)
    - T cells are more sensitive that other cells

- Sirolimus (Rapamycin)
  - inhibits lymphocyte proliferation and increases the number of Treg

Cyclosporin A and Tacrolimus

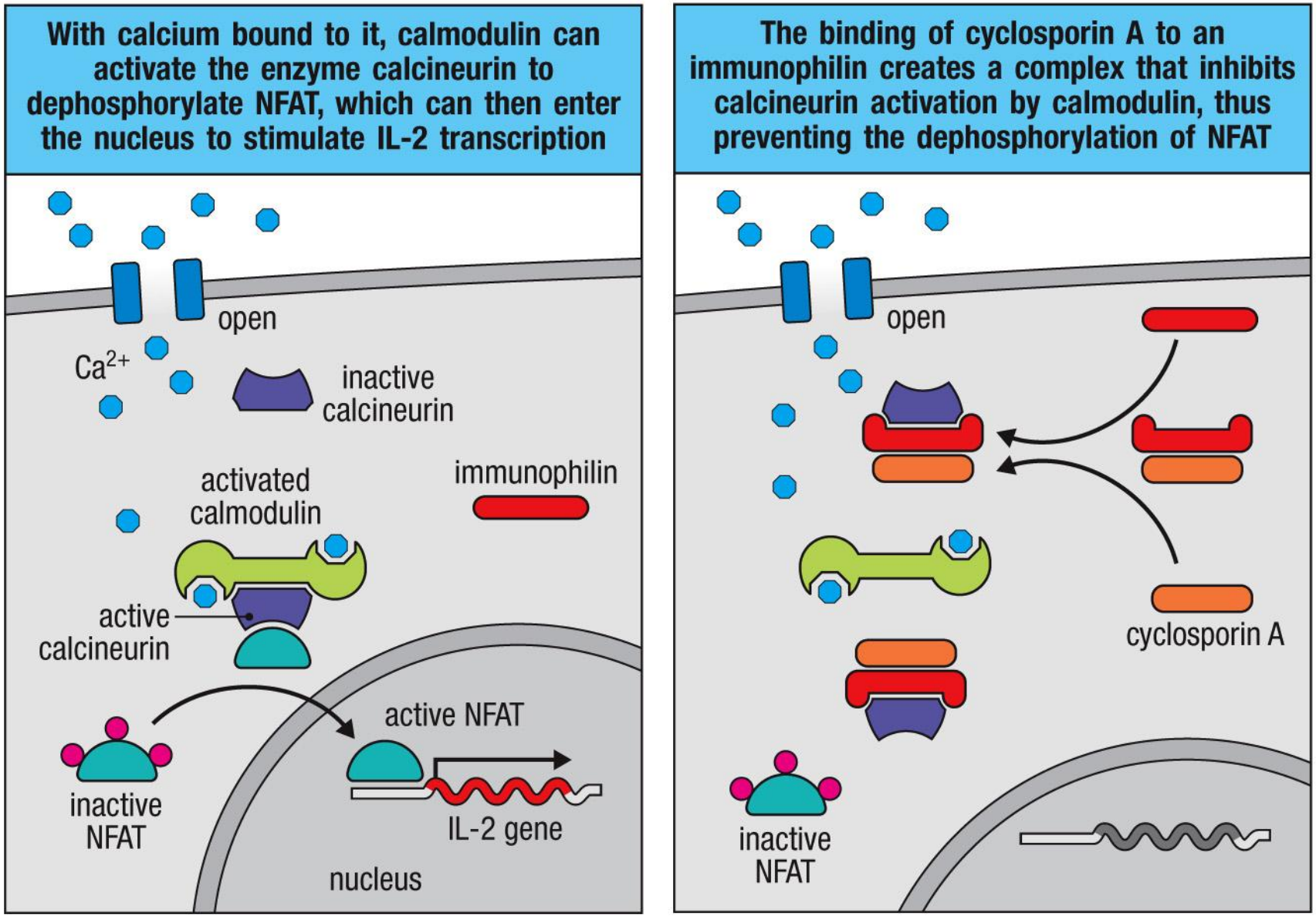


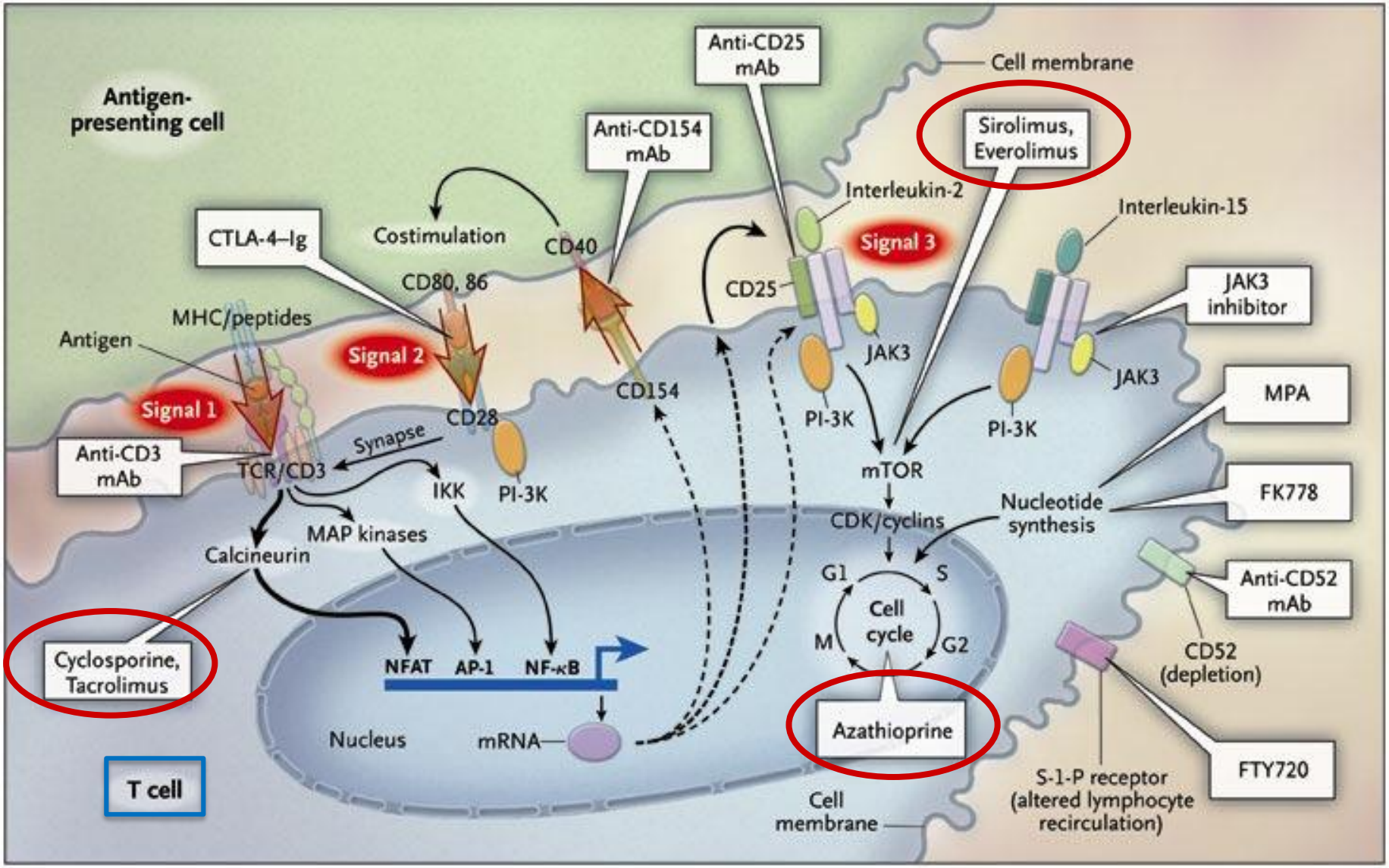
Figure 16.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Non cytotoxic Immunosupressive drugs

Immunological effects of cyclosporin A and tacrolimus	
Cell type	**Effects**
T lymphocyte	Reduced expression of IL-2, IL-3, IL-4, GM-CSF, TNF-α Reduced proliferation following decreased IL-2 production Reduced Ca^{2+}-dependent exocytosis of granule-associated serine esterases Inhibition of antigen-driven apoptosis
B lymphocyte	Inhibition of proliferation secondary to reduced cytokine production by T lymphocytes Inhibition of proliferation following ligation of surface immunoglobulin Induction of apoptosis following B-cell activation
Granulocyte	Reduced Ca^{2+}-dependent exocytosis of granule-associated serine esterases

Figure 16.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immunosupression



DOI: 10.1056/NEJMra033540

Antibodies in therapy

- Monoclonal antibody therapy: transplantations, autoimmune diseases (supression), tumors (stimulation)
  - **Cytotoxic** (antibody-mediated cytotoxicity)
  - **Neutralizing** (block the function of target molecule)
  - Usually produced in mice – problems?!?!?

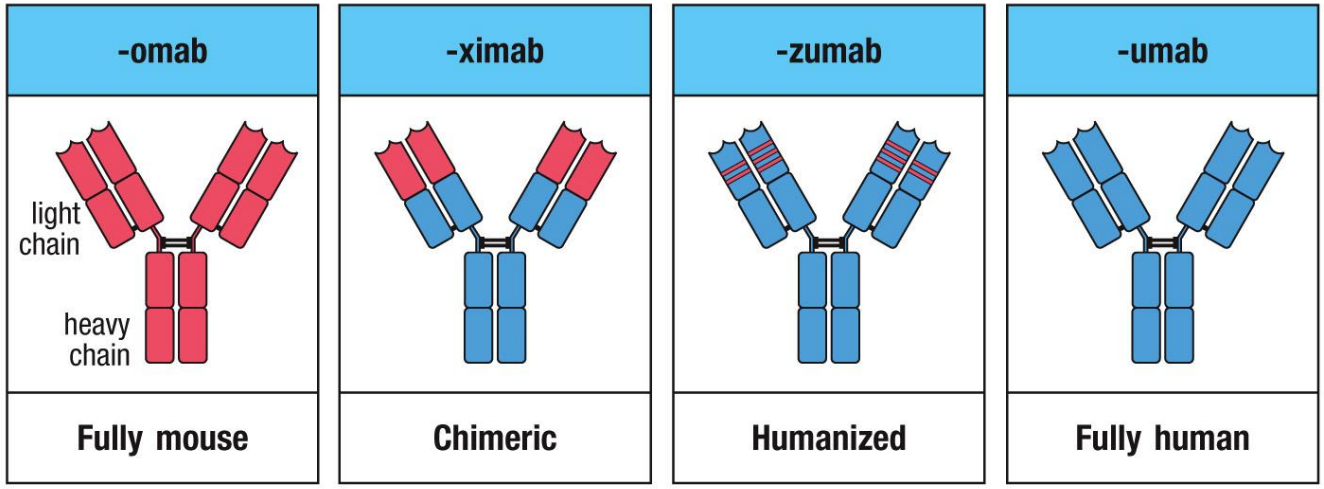


Figure 16.7 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

100% mouse 30% mouse 10% mouse 100% human

Examples:
-anti-CD3
-anti-TNF-a
-anti-IL-2
-anti-LFA1, ...

Monoclonal antibodies developed for immunotherapy			
Generic name	**Specificity**	**Mechanism of action**	**Approved indication**
Rituximab	Anti-CD20	Eliminates B cells	Non-Hodgkin's lymphoma
Alemtuzumab (Campath-1H)	Anti-CD52	Eliminates lymphocytes	Chronic myeloid leukemia
Muromomab (OKT3)	Anti-CD3	Inhibits T-cell activation	Kidney transplantation
Daclizumab	Anti-IL-2R	Reduces T-cell activation	
Basiliximab	Anti-IL-2R	Reduces T-cell activation	
Infliximab	Anti-TNF-α	Inhibit inflammation induced by TNF-α	Crohn's disease
Certolizumab	Anti-TNF-α		Rheumatoid arthritis
Adalimumab	Anti-TNF-α		
Golimumab	Anti-TNF-α		
Tocilizumab	Anti-IL-6R	Blocks inflammation induced by IL-6 signaling	
Canakinumab	Anti-IL-1β	Blocks inflammation caused by IL-1	Muckle–Wells syndrome
Denosumab	Anti-RANK-L	Inhibits activation of osteoclasts by RANK-L	Bone loss
Ustekinumab	Anti-IL-12/23	Inhibits inflammation caused by IL-12 and IL-23	Psoriasis
Efalizumab	Anti-CD11a (α_L integrin subunit)	Block lymphocyte trafficking	Psoriasis (withdrawn from use in United States and European Union)
Natalizumab	Anti-α_4 integrin		Multiple sclerosis
Omalizumab	Anti-IgE	Removes IgE antibody	Chronic asthma
Belimumab	Anti-BLyS	Reduces B-cell responses	Systemic lupus erythematosus (pending approval)
Ipilimumab	Anti-CTLA-4	Increases CD4 T-cell responses	Metastatic melanoma
Raxibacumab	Anti-*Bacillus anthracis* protective antigen (the cell-binding moiety of anthrax toxin)	Prevents action of anthrax toxins	Anthrax infection (pending approval)

Figure 16.8 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Anti-CD4 Ab & graft tolerance

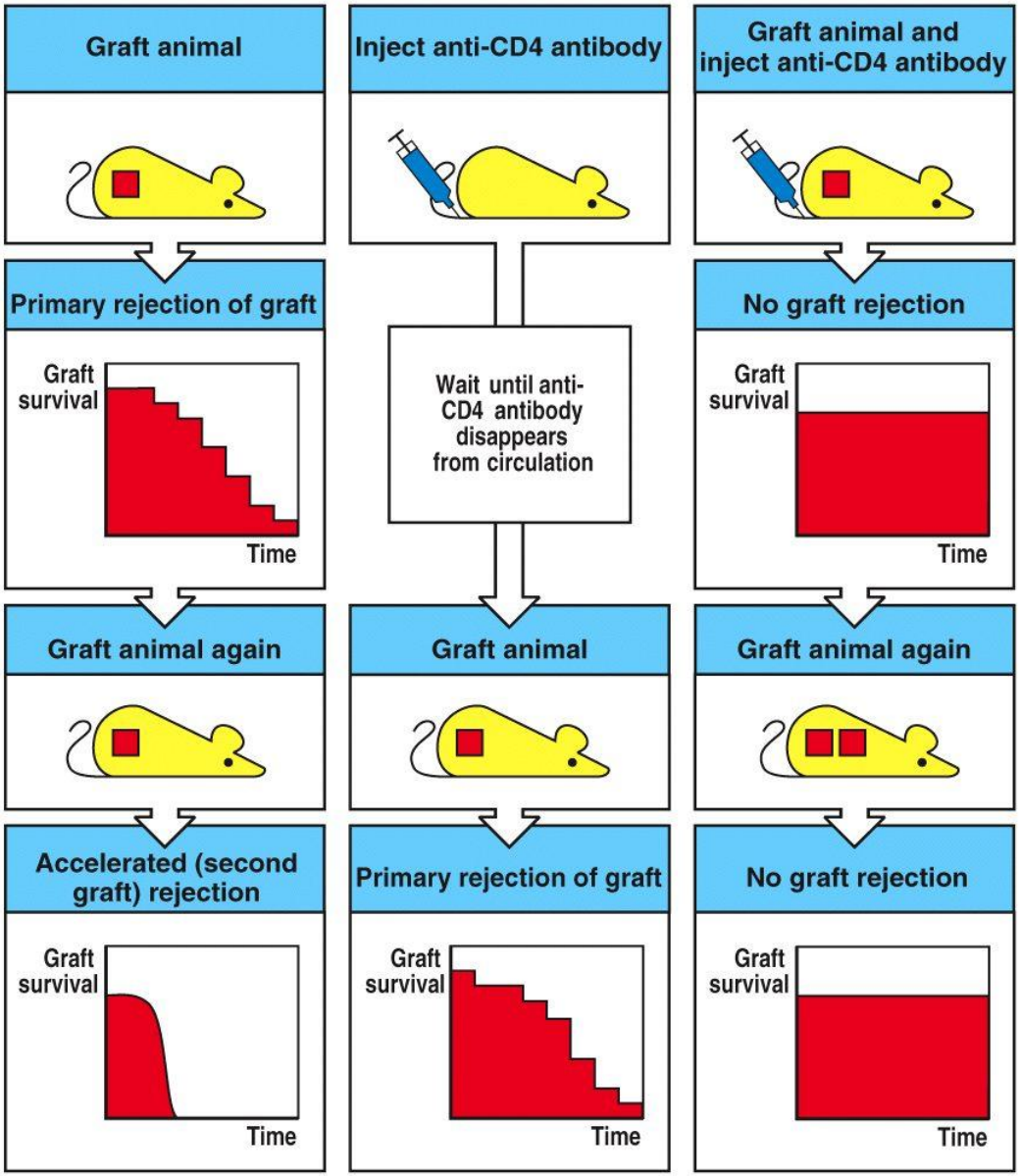


Figure 14-6 Immunobiology, 6/e. (© Garland Science 2005)

Anti-TNFa Ab in autoimmune diseases

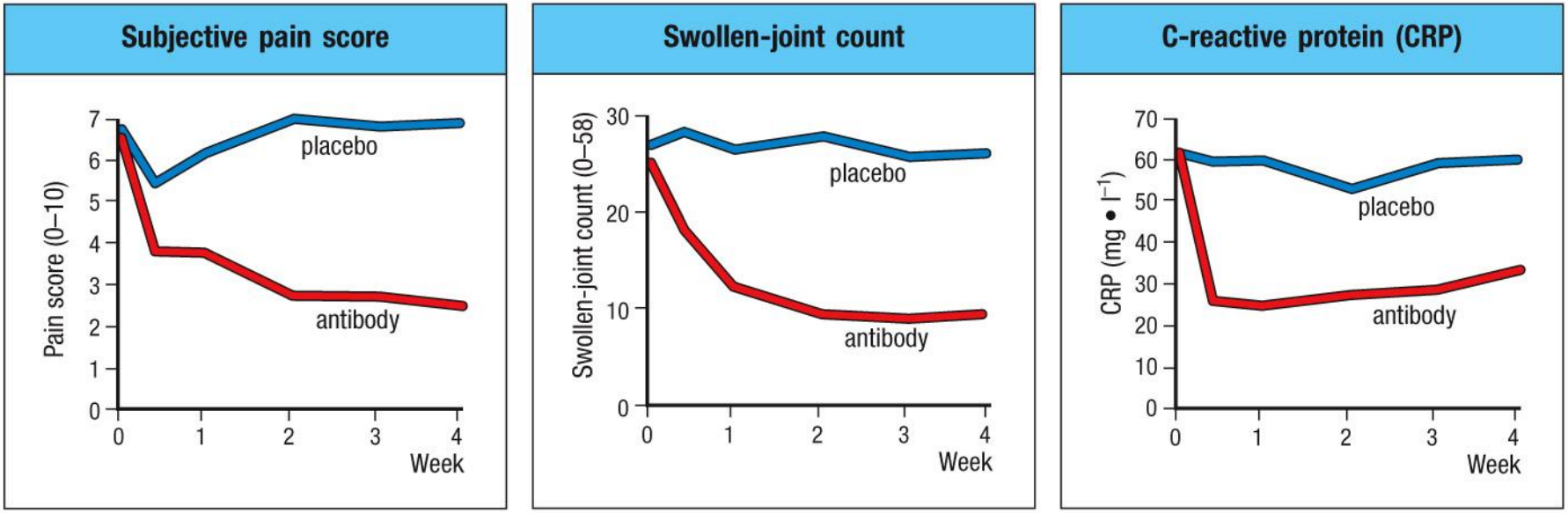


Figure 16.9 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Works well for: Rheumatoid arthritis, Crohn's disease, ankylosing spondylitis

Does not work for: multiple sclerosis

Anti-integrin Ab im MS

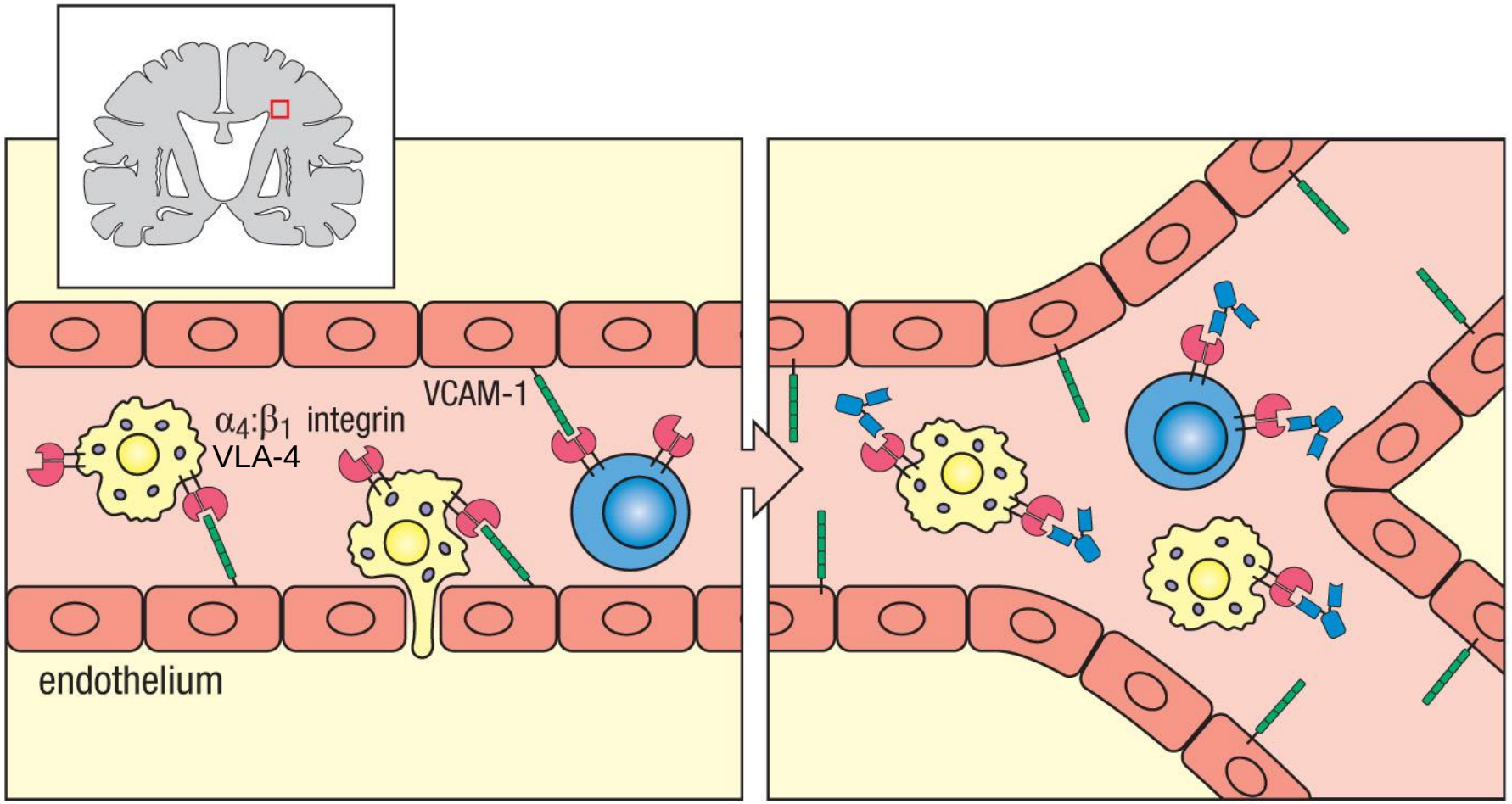


Figure 16.10 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immune responses and tumors

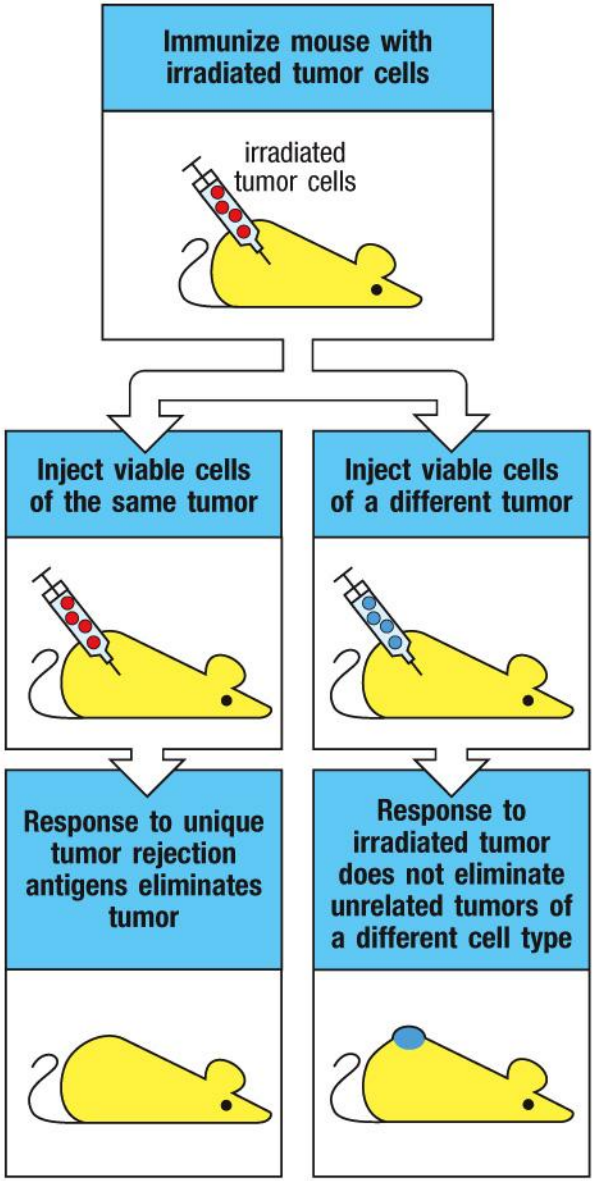


Figure 16.12 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Malignant cells are monitored by immune system

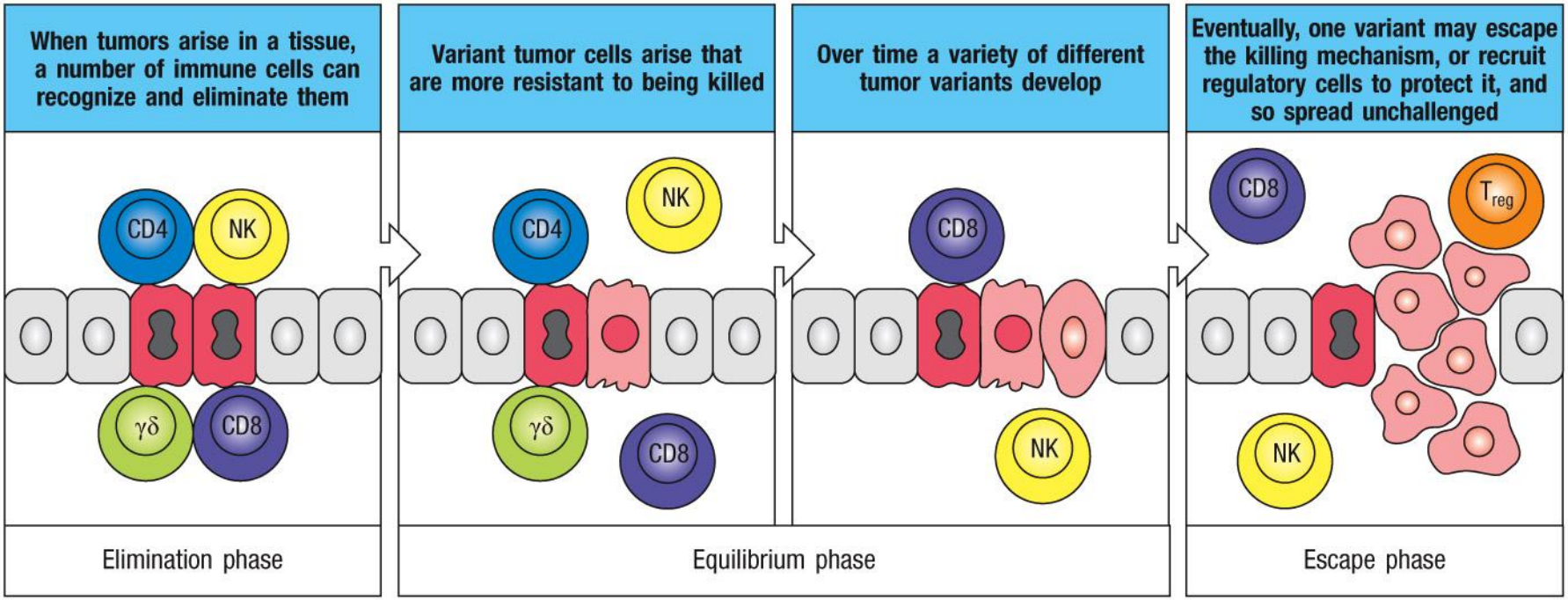


Figure 16.13 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Tumors can avoid immune recognition

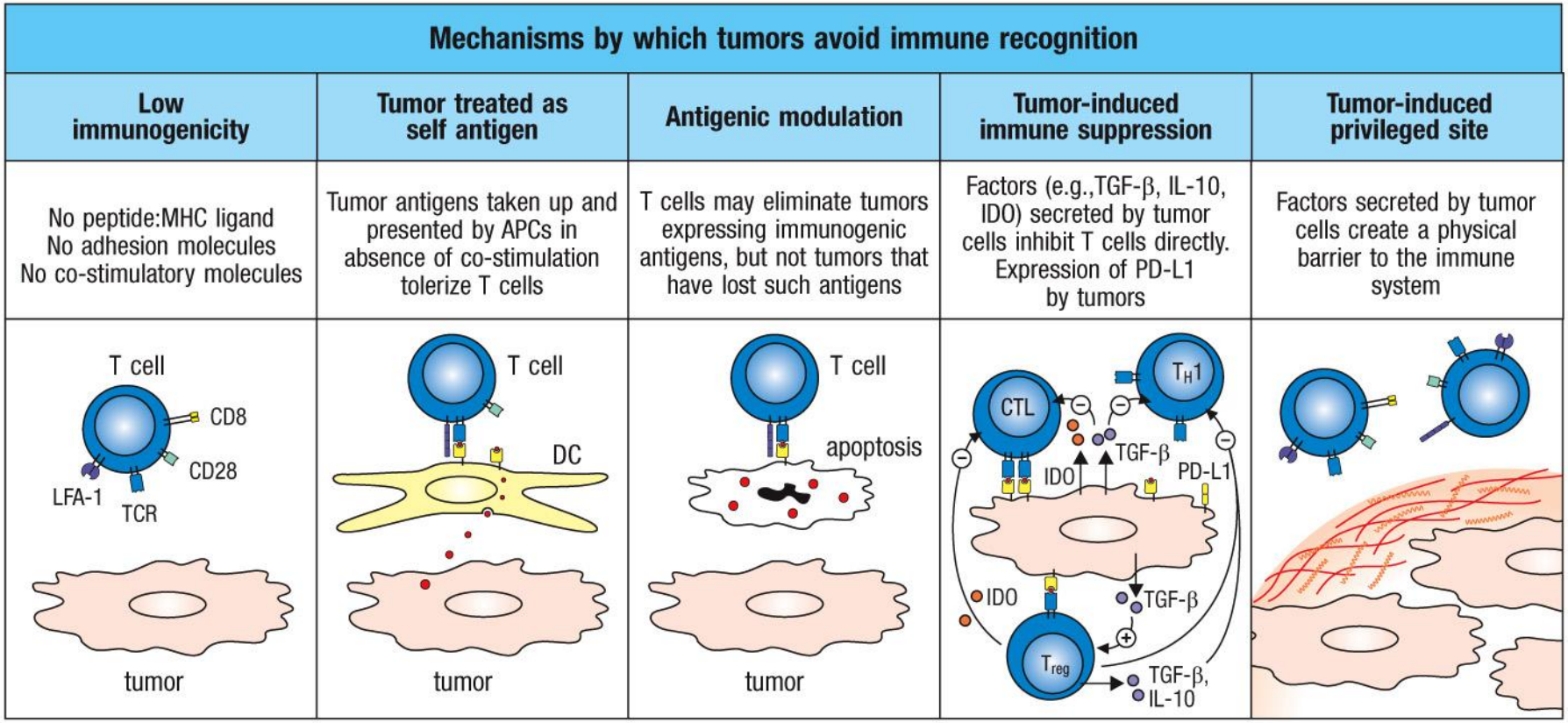


Figure 16.14 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Escaping immune surveillance

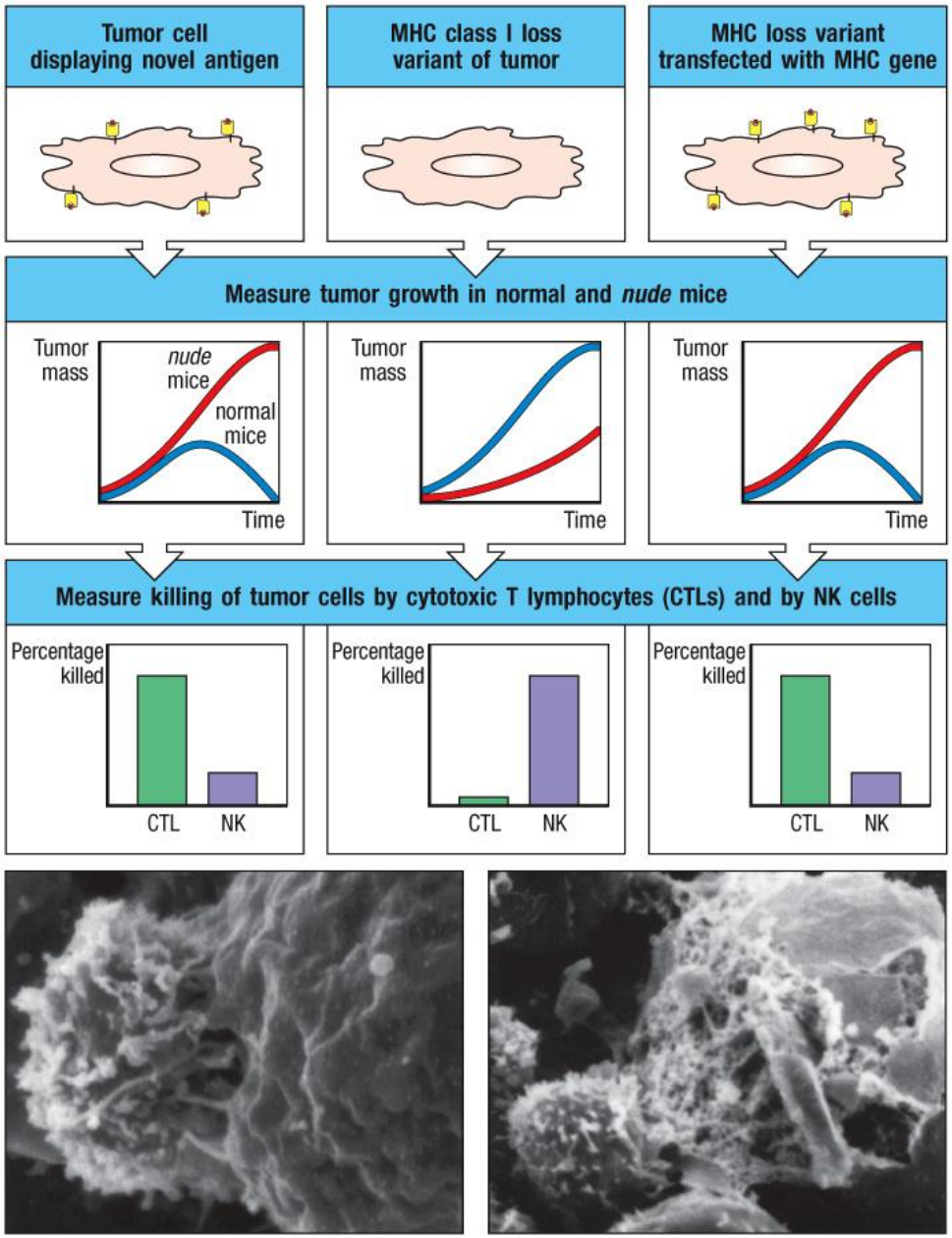


Figure 16.16 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

mAbs and tumors

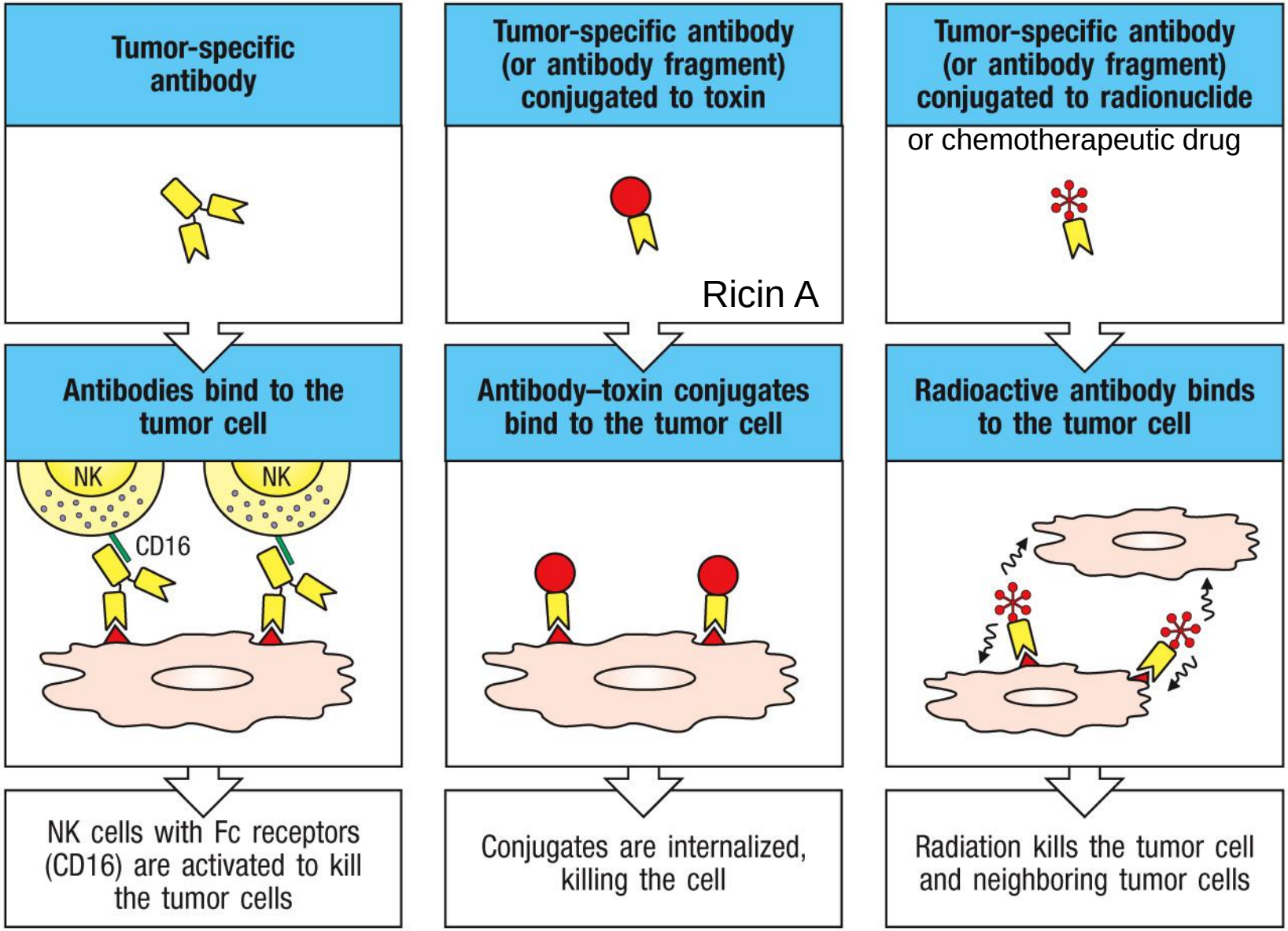
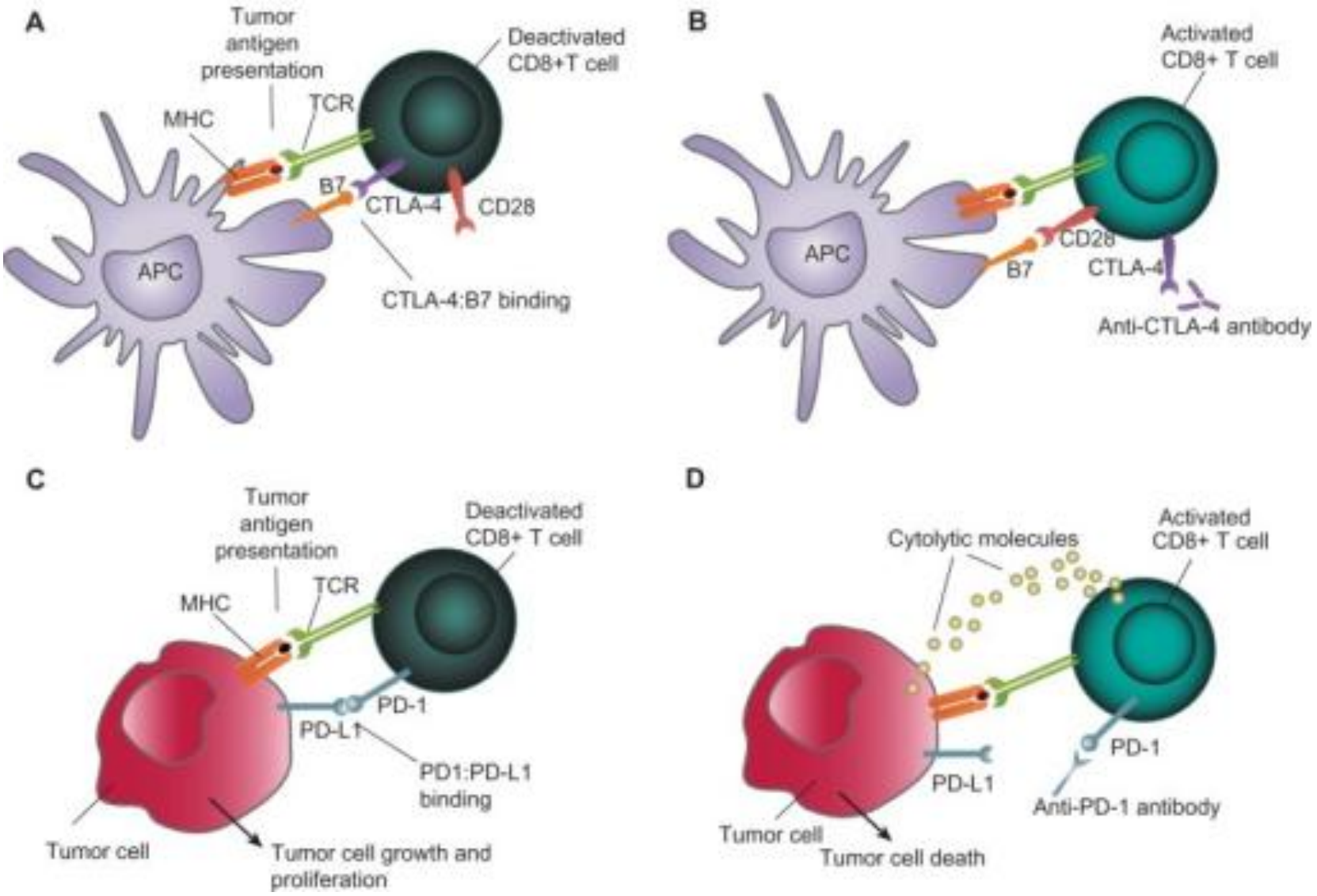


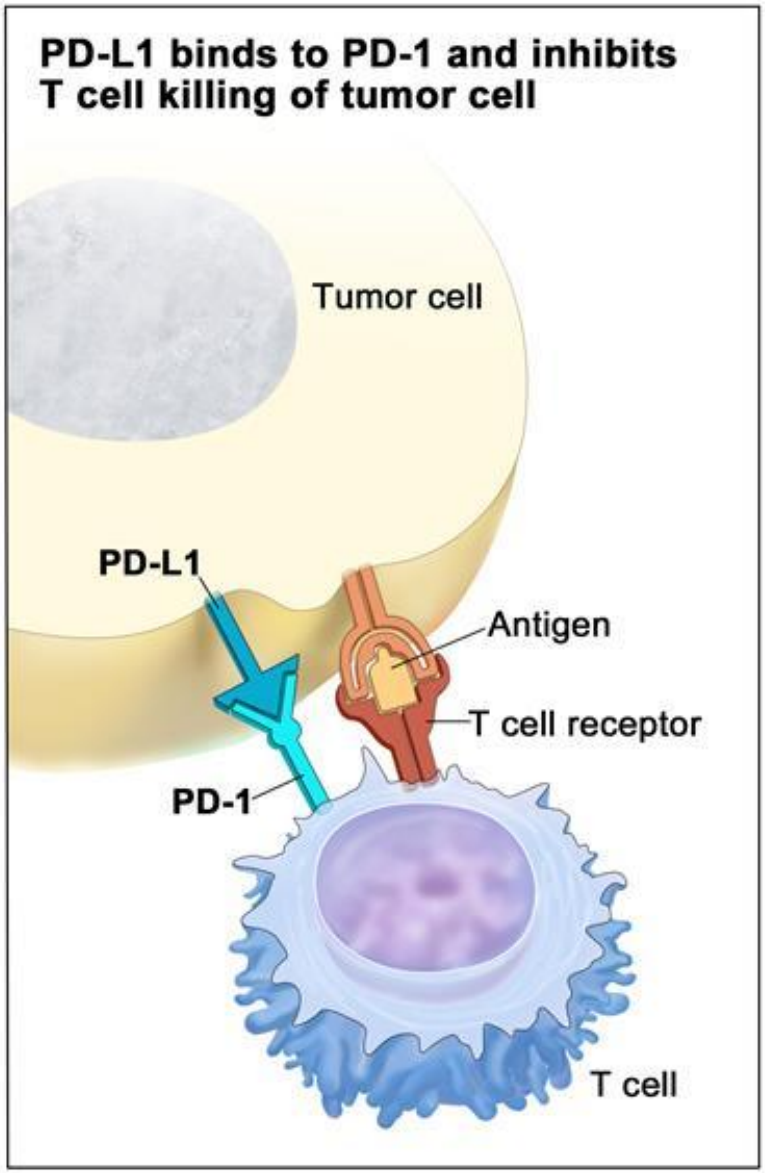
Figure 16.19 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

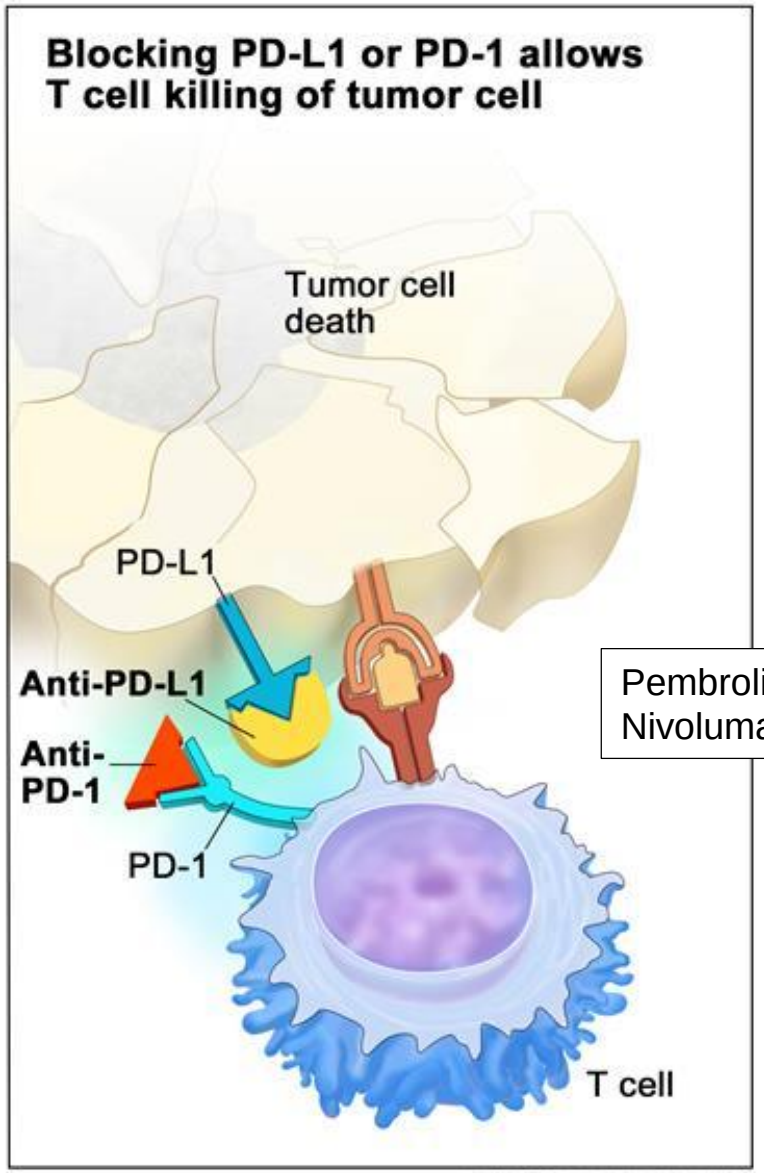
Checkpoint blockade: anti CTLA-4 and anti-PD-1



https://doi.org/10.4137/CMO.S34540

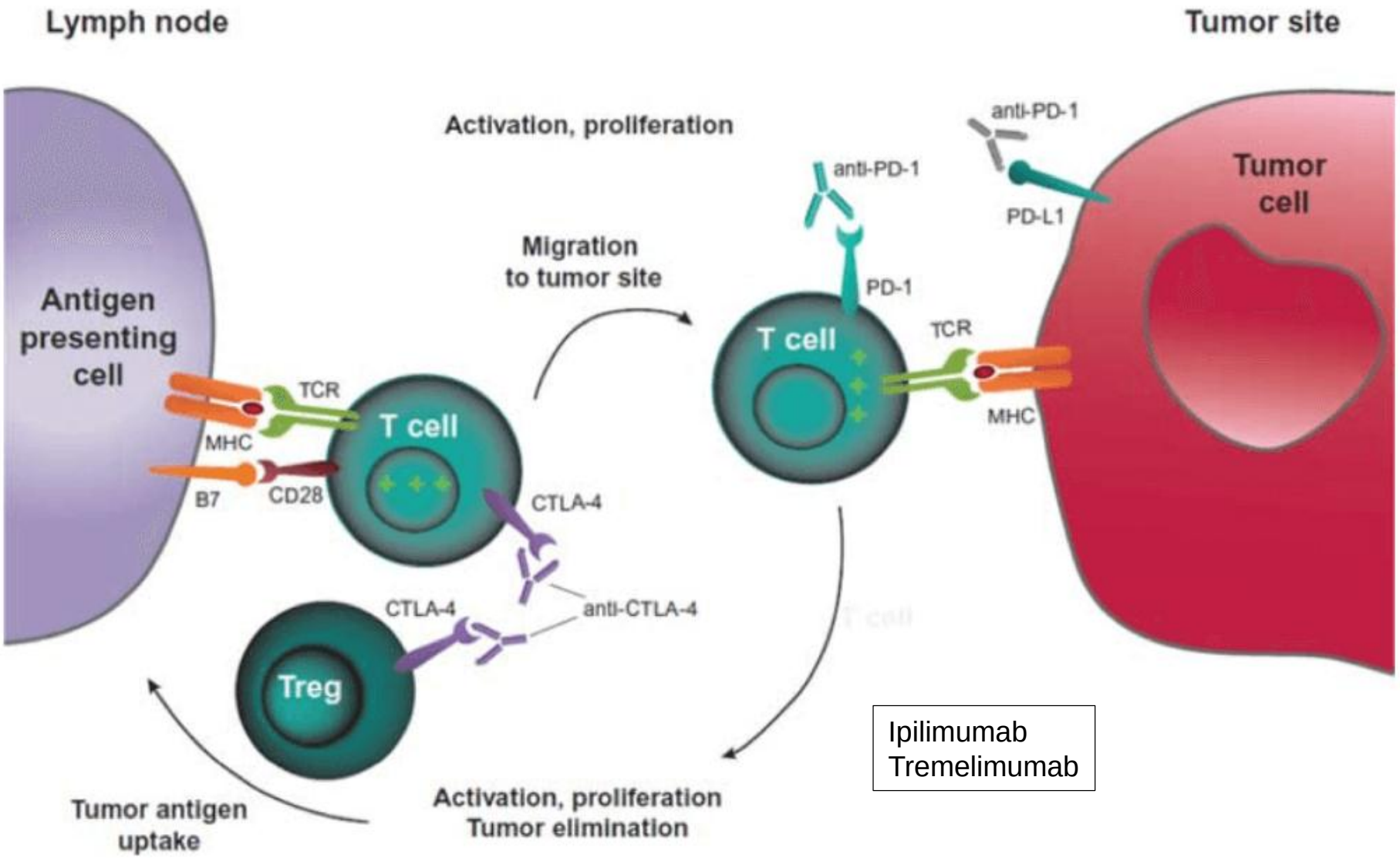
Anti PD-1



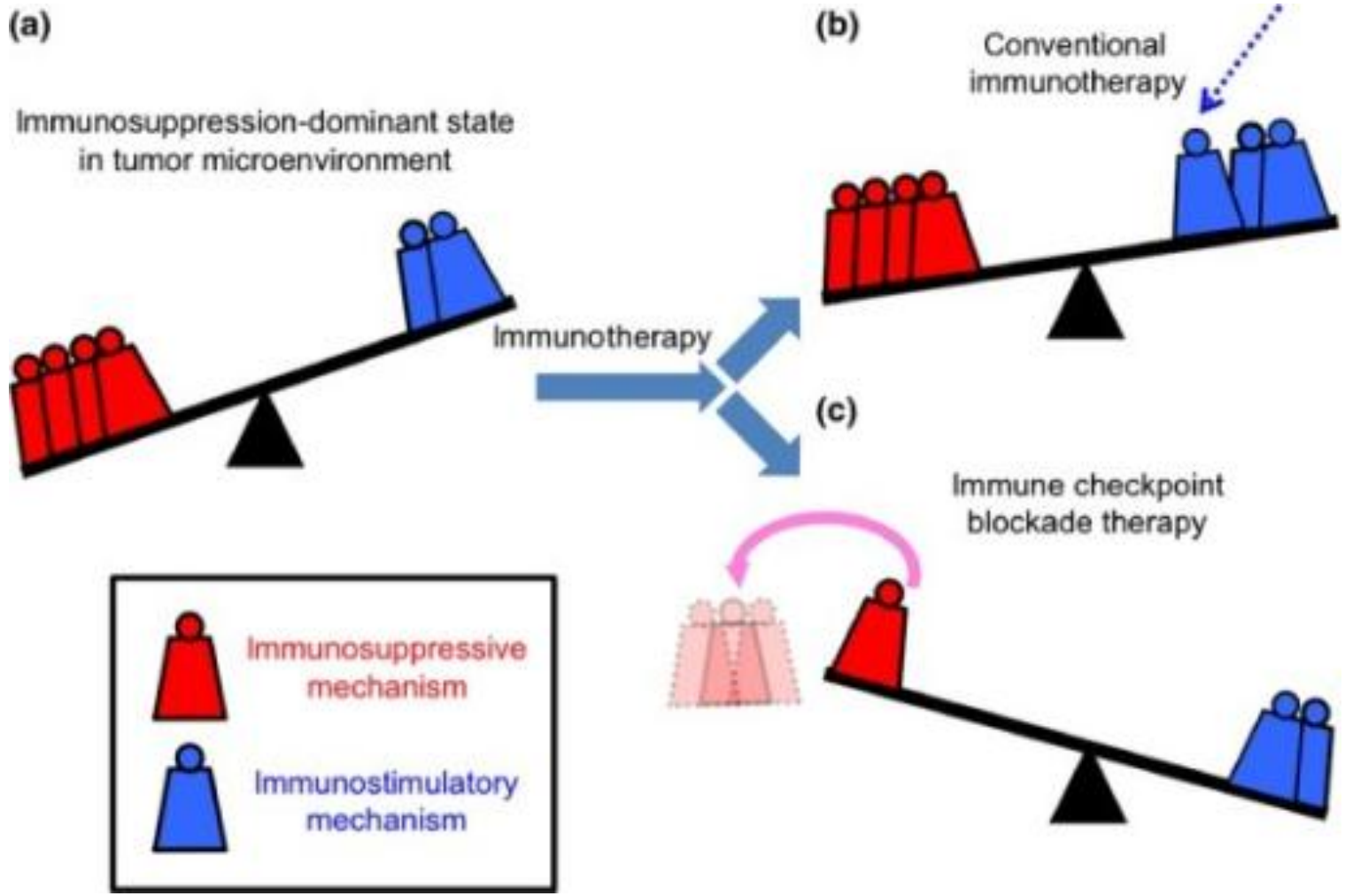


Pembrolizumab
Nivolumab

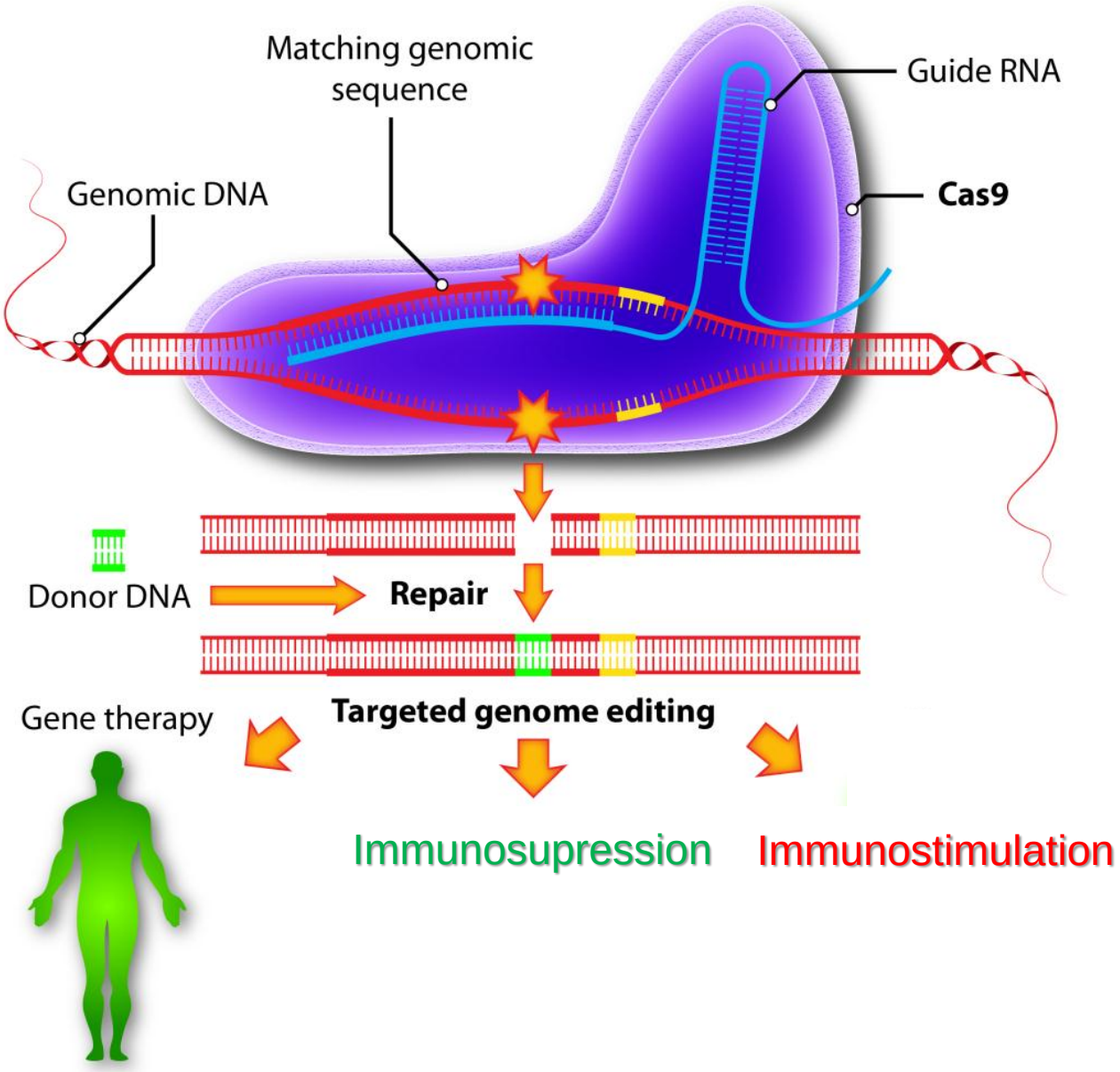
Anti CTLA-4


Lymph node
Tumor site
Activation, proliferation
Migration
to tumor site
Antigen
presenting
cell
TCR
MHC
B7
CD28
T cell
CTLA-4
anti-CTLA-4
CTLA-4
Treg
anti-PD-1
anti-PD-1
PD-L1
Tumor
cell
PD-1
T cell
TCR
MHC
Tumor antigen
uptake
Activation, proliferation
Tumor elimination
Ipilimumab
Tremelimumab

Modern concepts of tumour immunotherapy



CRISPR/Cas9


Matching genomic sequence
Guide RNA
Genomic DNA
Cas9
Donor DNA
Repair
Gene therapy
Targeted genome editing
Immunosupression
Immunostimulation

Immunostimulation

When?

- Tumors
- Prevention of pathogenic infections

- **Specific immunostimulants**
  - antibodies or antigens
  - Vaccines
- **Non-specific immunostimulants**
  - adjuvants
  - non-specific immunostimulators

Problems:

- Unknown effects (novel methods and aproaches)
- Autoimmunity?