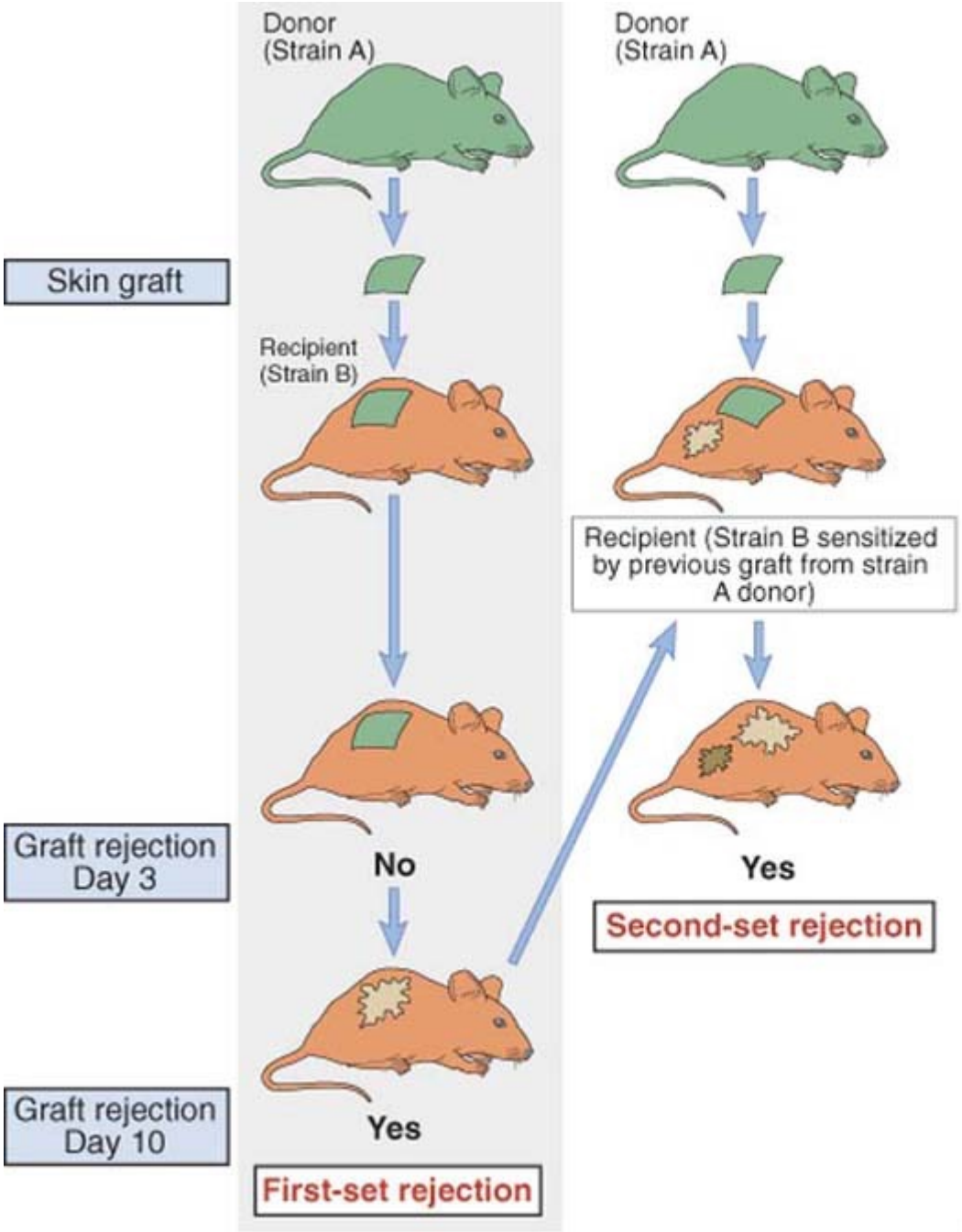
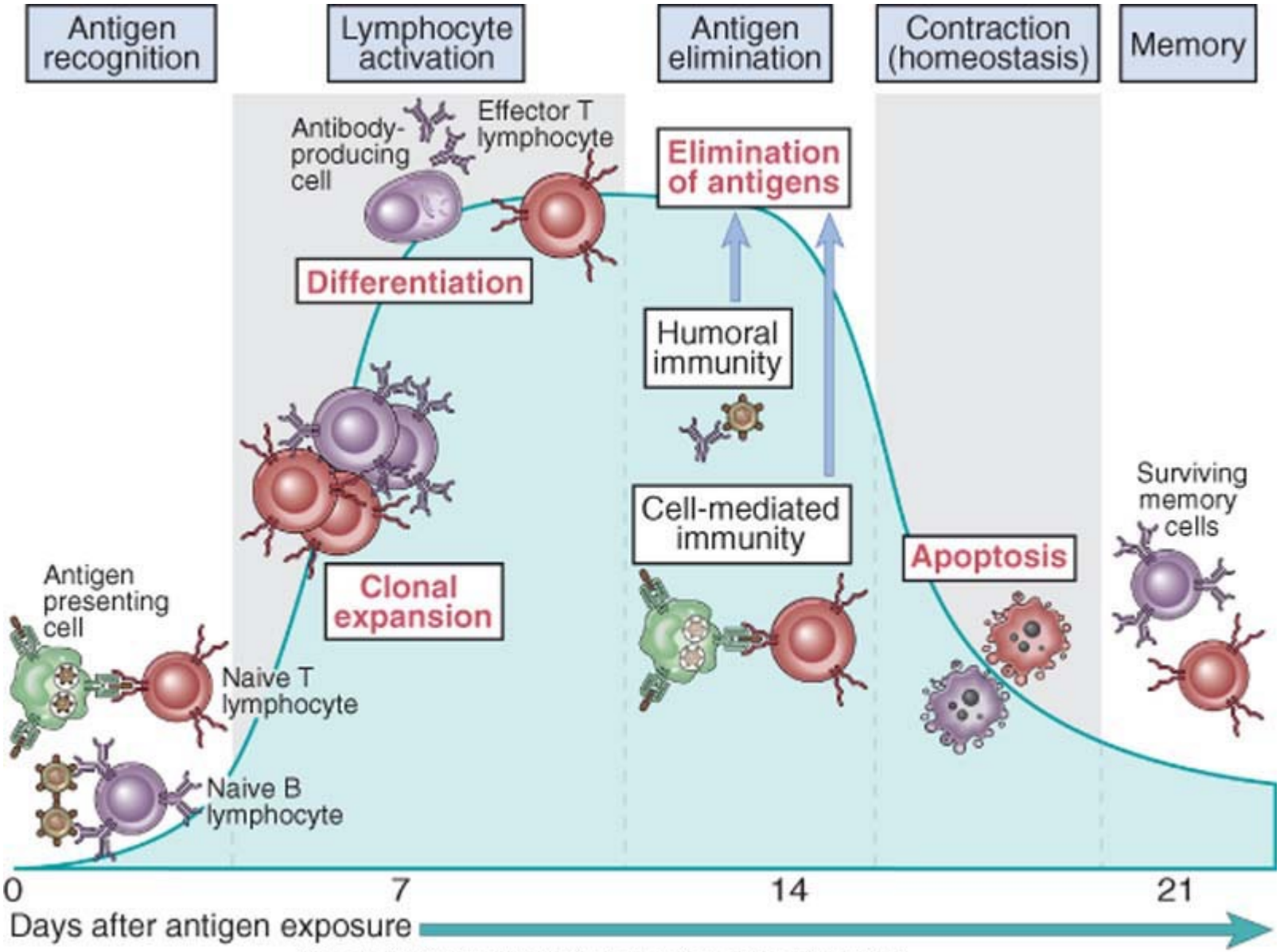
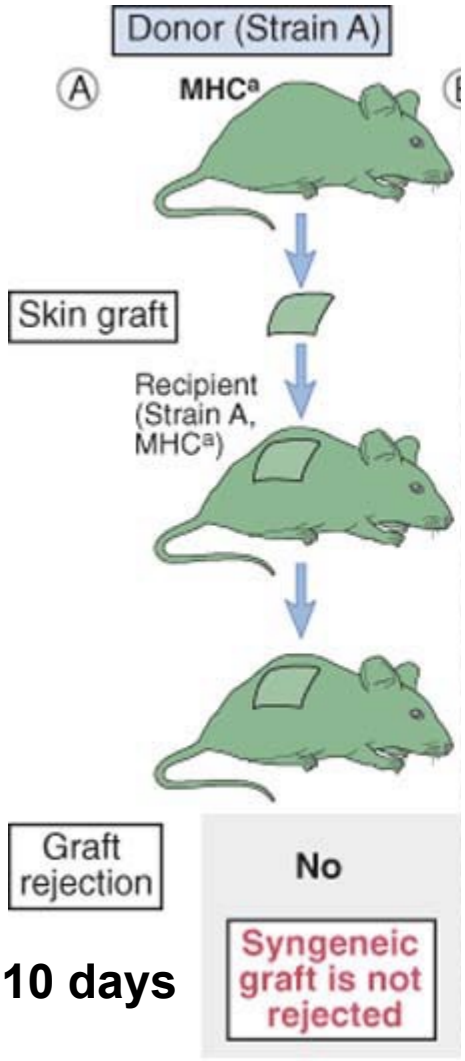
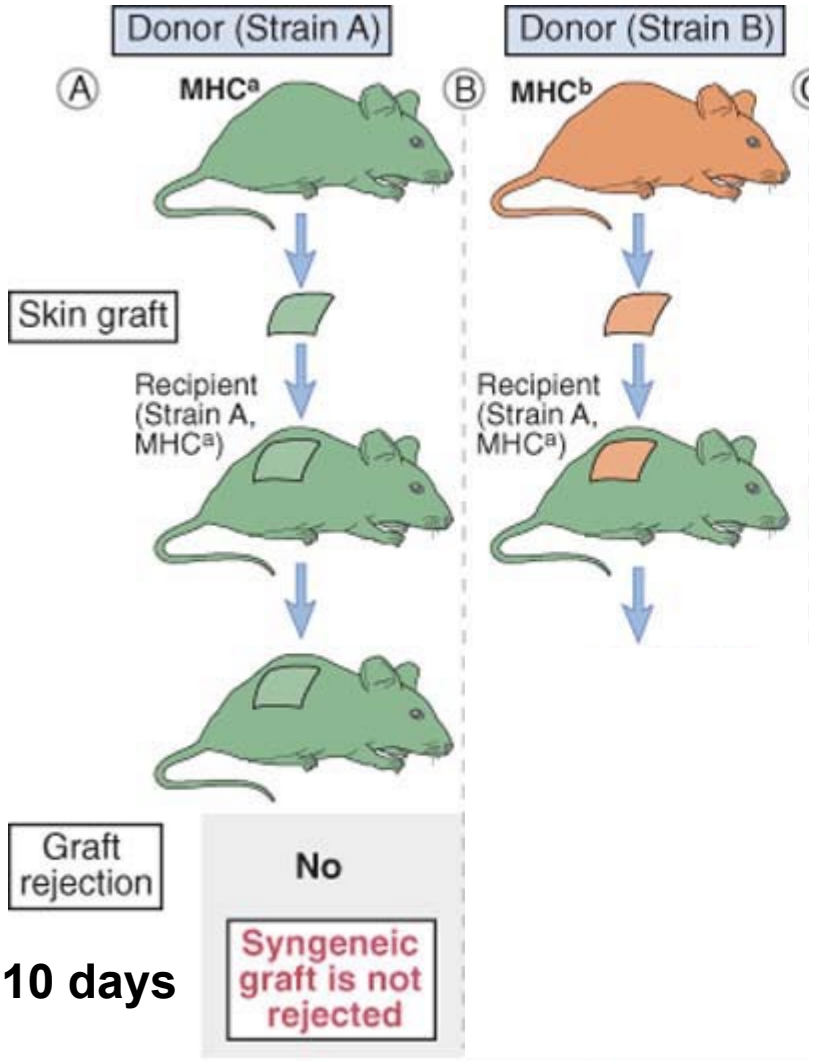
Immunology and transplantation

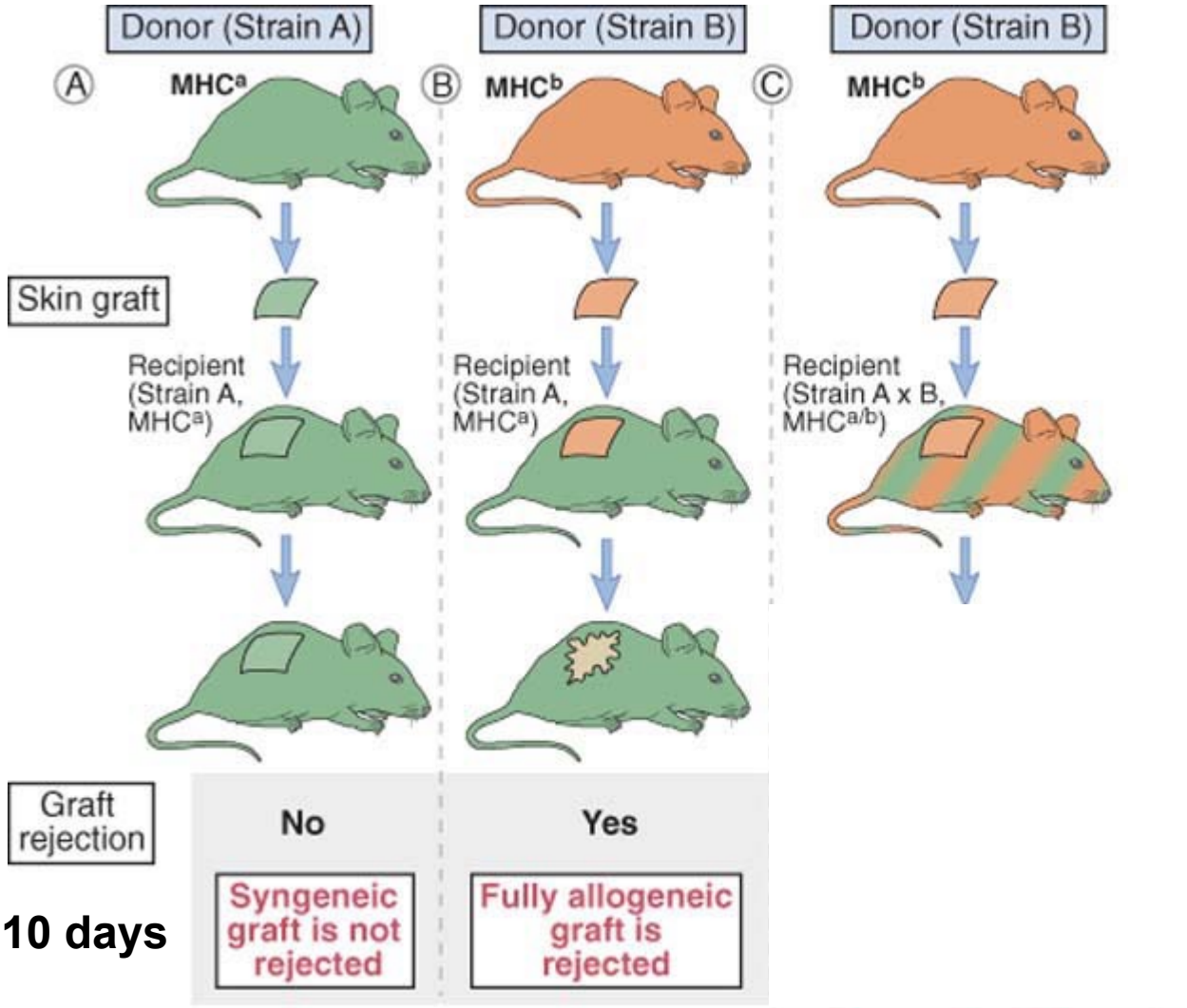


Phases of the adaptive immune response

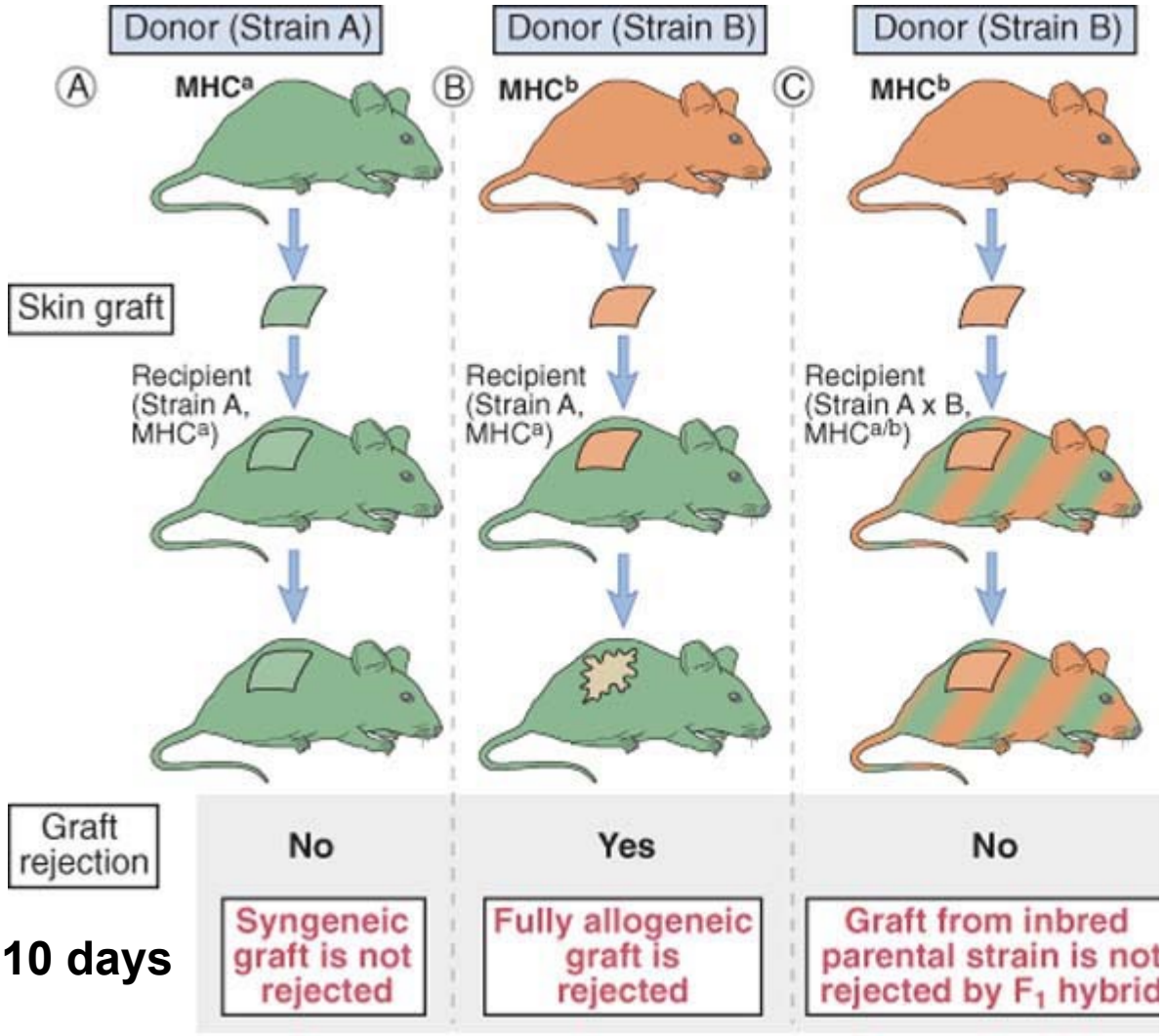




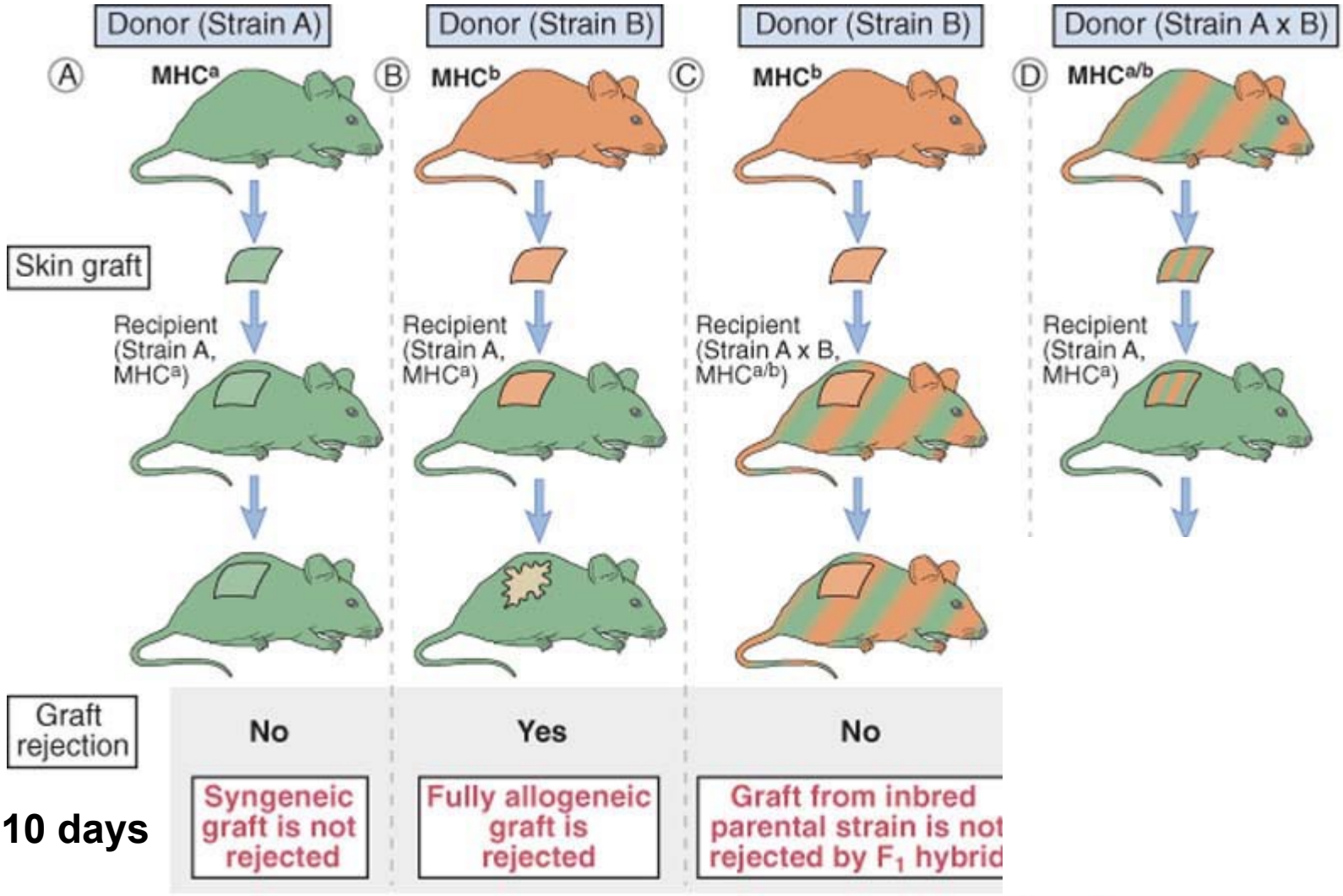


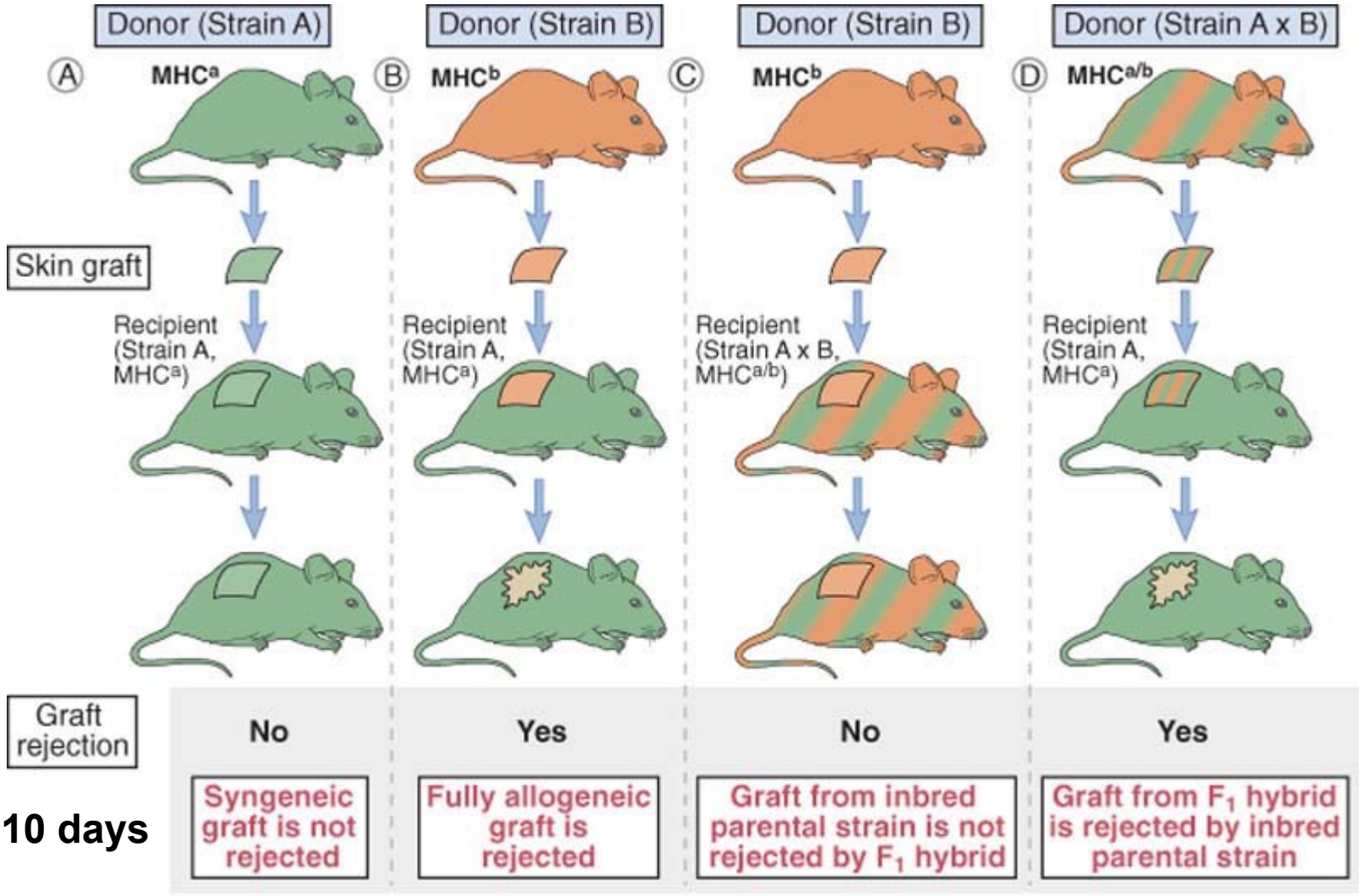


10 days

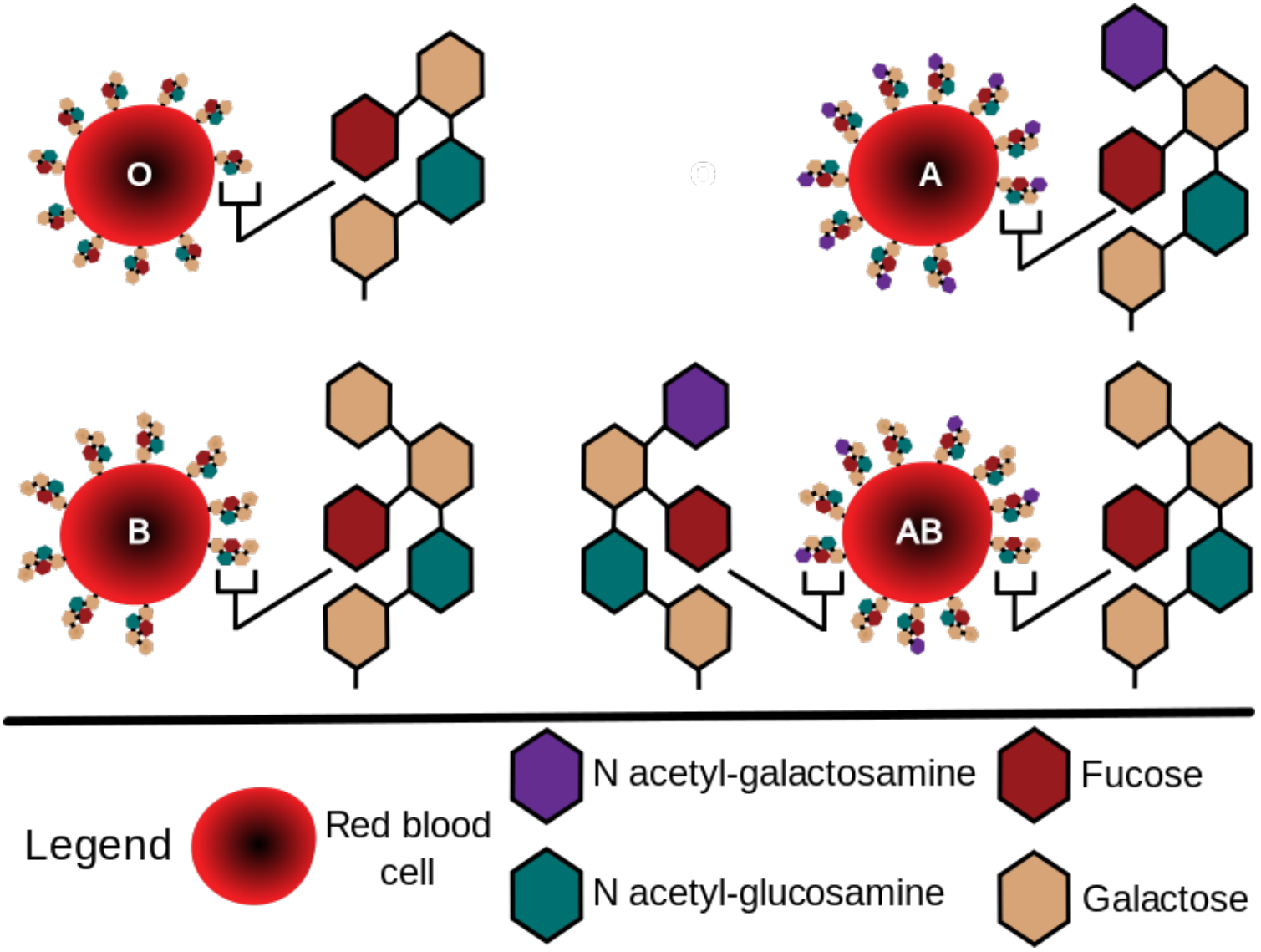


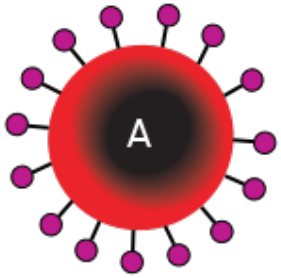
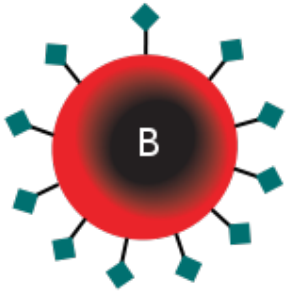
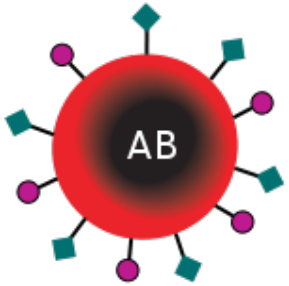
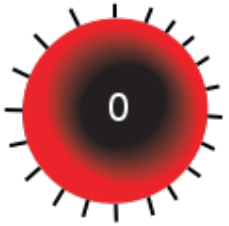
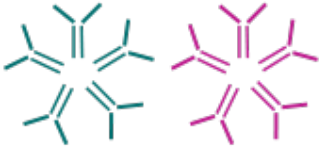
10 days



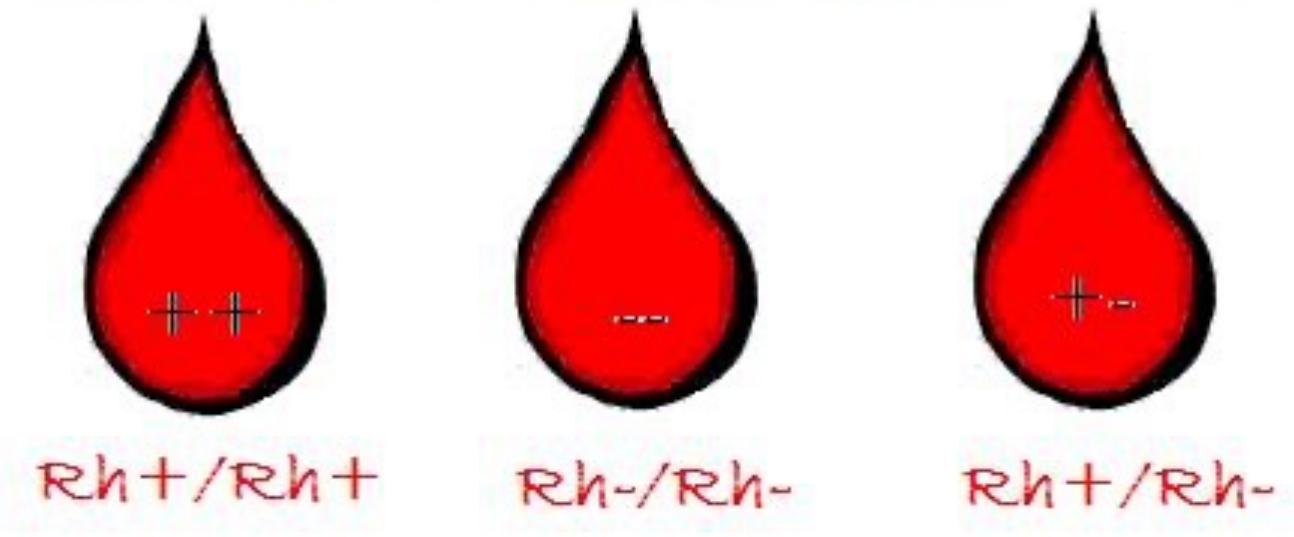


Ag del sistema AB0



	Gruppo A	Gruppo B	Gruppo AB	Gruppo 0
Tipi di GLOBULI ROSSI				
Anticorpi presenti	 Anti-B	 Anti-A	Nessuno	 Anti-A e Anti-B
Antigeni presenti	 A	 B	 A e B	Nessuno

Ag Rhesus (Rh)



Human Leukocyte Antigens (HLA)

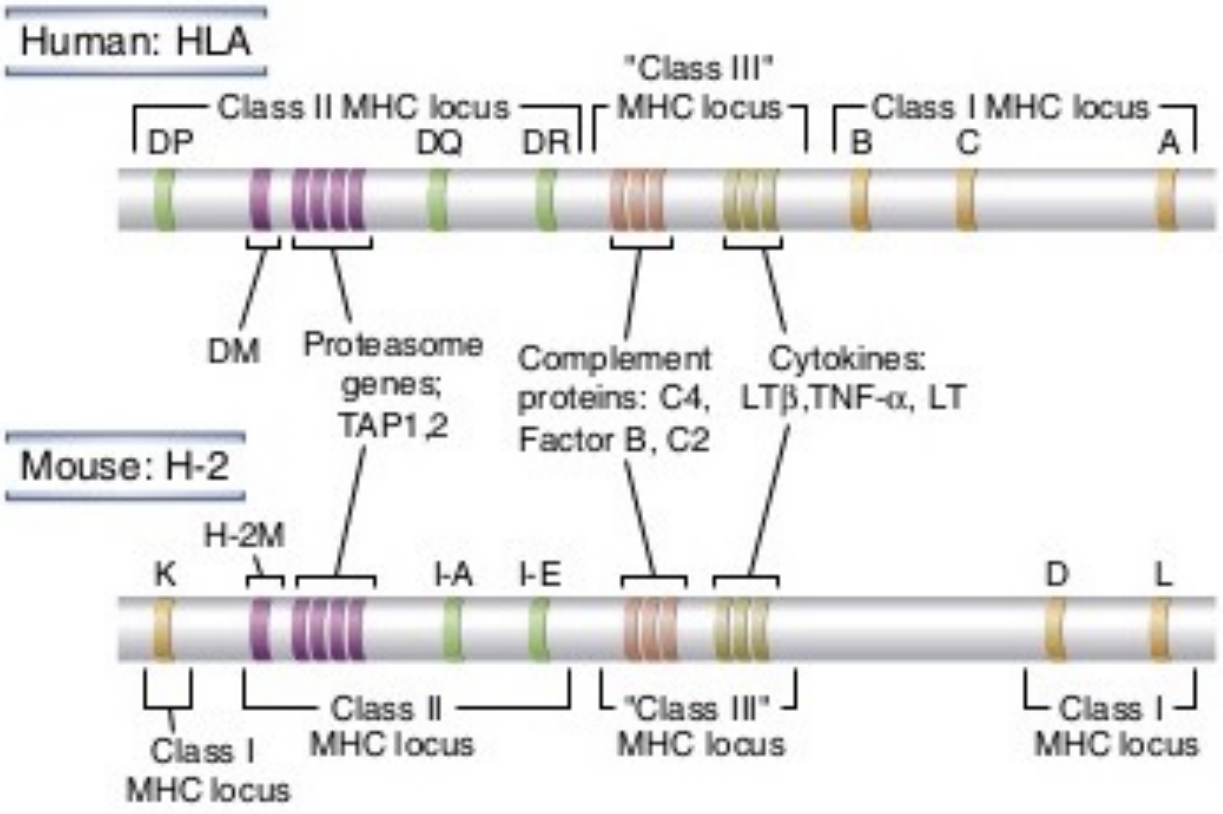


FIGURE 6-7 Schematic maps of human and mouse MHC loci. The basic organization of the genes in the MHC locus is similar in humans and mice. Sizes of genes and intervening DNA segments are not shown to scale. Class II loci are shown as single blocks, but each locus consists of several genes. "Class III" MHC locus refers to genes that encode molecules other than peptide-display molecules; this term is not used commonly.

Chromosome 6

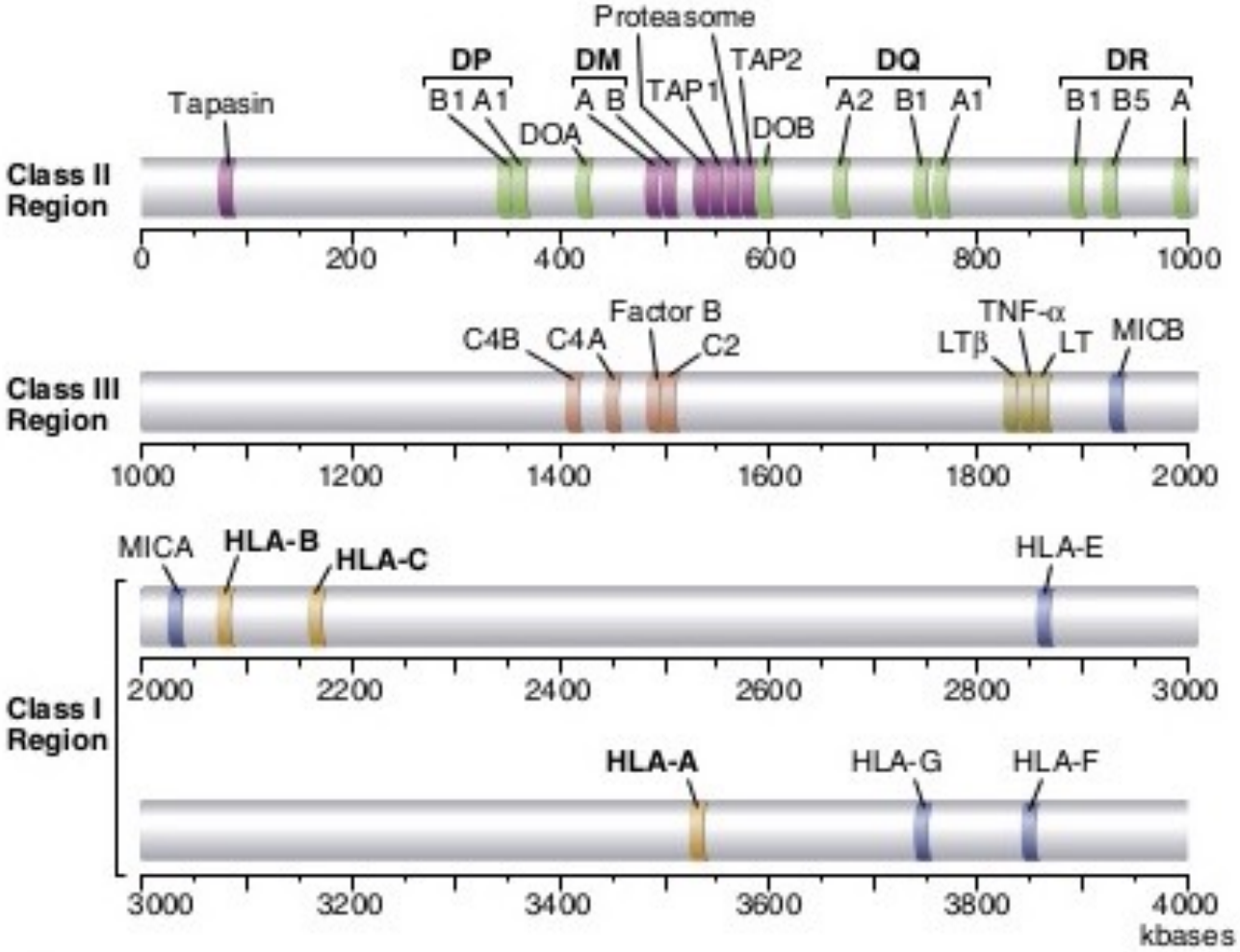


FIGURE 6-8 Map of the human MHC. The genes located within the human MHC locus are illustrated. In addition to the class I and class II *MHC* genes, *HLA-E*, *HLA-F*, and *HLA-G and the MIC* genes encode class I-like molecules, many of which are recognized by NK cells; *C4*, *C2*, and *Factor B* genes encode complement proteins; tapasin, DM, DO, TAP, and proteasome encode proteins involved in antigen processing; LTα, LTβ, and TNF encode cytokines. Many pseudogenes and genes whose roles in immune responses are not established are located in the HLA complex but are not shown to simplify the map.

Class I MHC

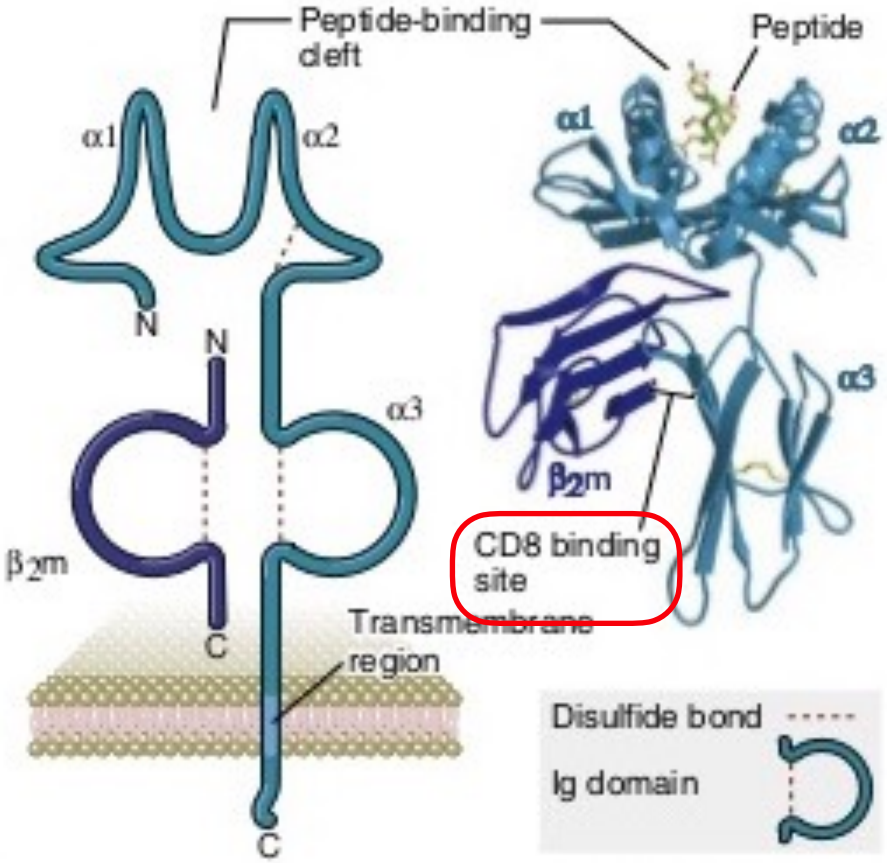


FIGURE 6-10 Structure of a class I MHC molecule. The schematic diagram *(left)* illustrates the different regions of the MHC molecule (not drawn to scale). Class I molecules are composed of a polymorphic α chain non-covalently attached to the non-polymorphic β_2-microglobulin (β_2m). The α chain is glycosylated; carbohydrate residues are not shown. The ribbon diagram *(right)* shows the structure of the extracellular portion of the HLA-B27 molecule with a bound peptide, resolved by x-ray crystallography. *(Courtesy of Dr. P. Bjorkman, California Institute of Technology, Pasadena.)*

Class II MHC

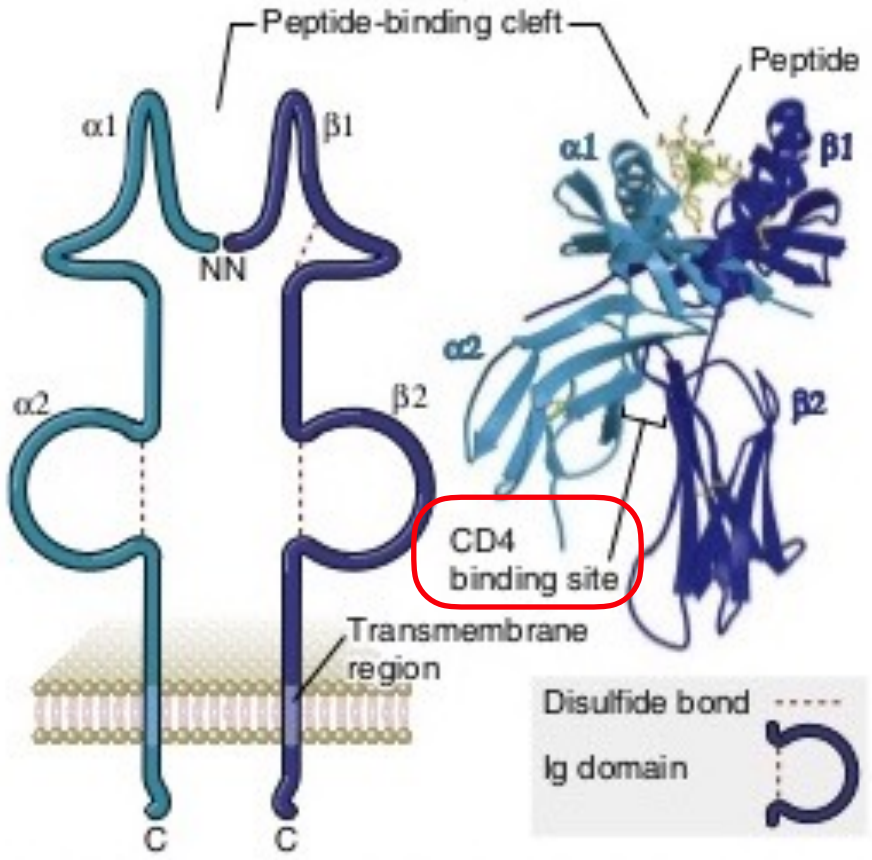
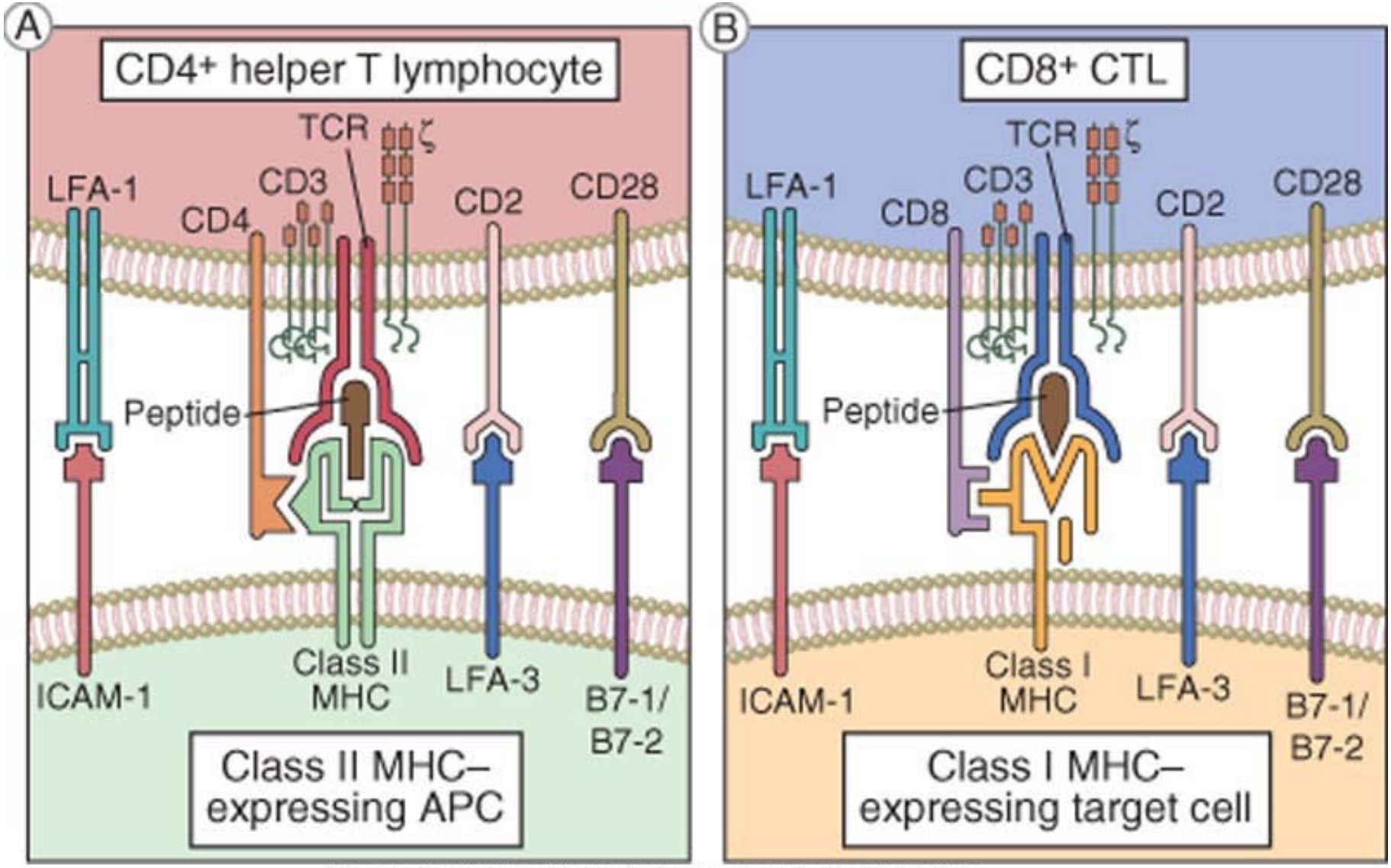


FIGURE 6-12 Structure of a class II MHC molecule. The schematic diagram *(left)* illustrates the different regions of the MHC molecule (not drawn to scale). Class II molecules are composed of a polymorphic α chain non-covalently attached to a polymorphic β chain. Both chains are glycosylated; carbohydrate residues are not shown. The ribbon diagram *(right)* shows the structure of the extracellular portion of the HLA-DR1 molecule with a bound peptide, resolved by xray crystallography. *(Courtesy of Dr. P. Bjorkman, California Institute of Technology, Pasadena.)*



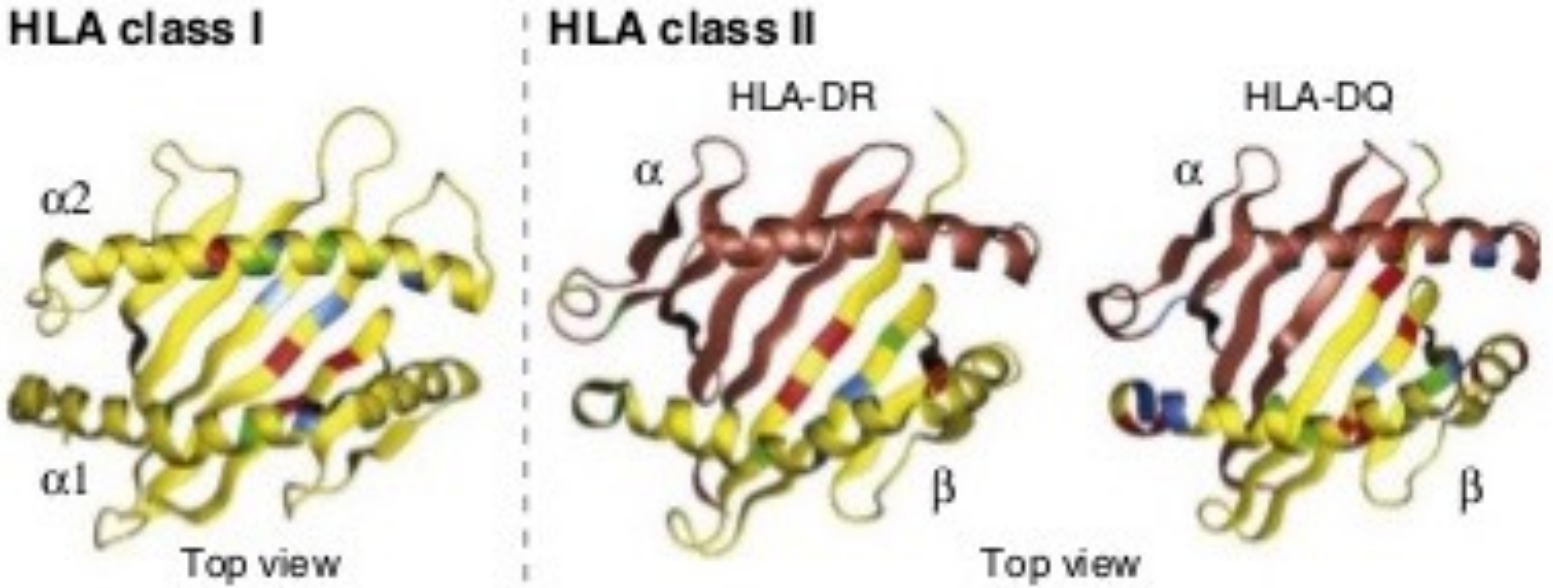


FIGURE 6-11 Polymorphic residues of MHC molecules. The polymorphic residues of class I and class II MHC molecules are located in the peptide-binding clefts and the α helices around the clefts. The regions of greatest variability among different HLA alleles are indicated in red, of intermediate variability in green, and of the lowest variability in blue. *(Reproduced with permission from Margulies DH, Natarajan K, Rossjohn J, McCluskey J: Major histocompatibility complex [MHC] molecules: structure, function, and genetics. In Paul WE [ed]: Fundamental immunology, 6th ed, Philadelphia, 2008, Lippincott Williams & Wilkins.)*

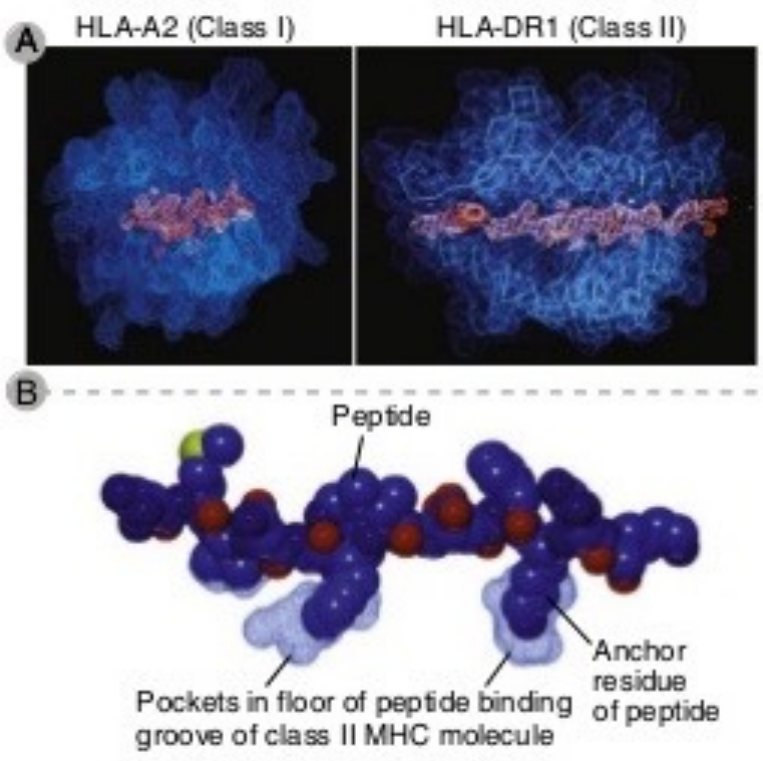
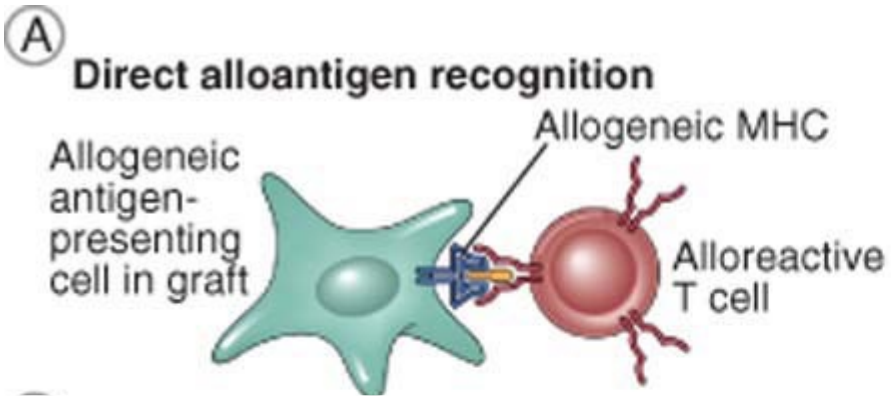


TABLE 6-4 Features of Class I and Class II MHC Molecules

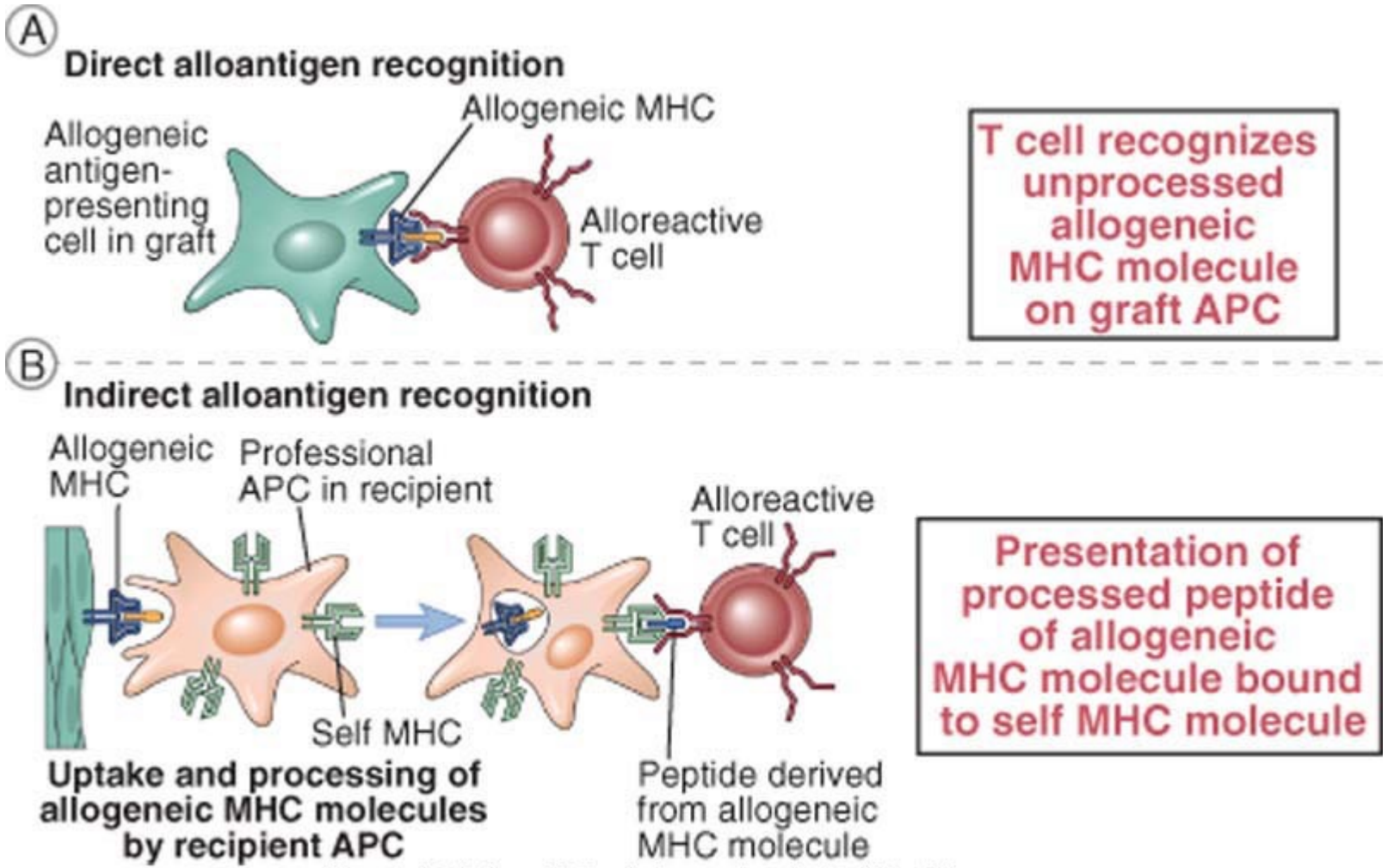
Feature	Class I MHC	Class II MHC
Polypeptide chains	α β_2-microglobulin	α and β
Locations of polymorphic residues	α1 and α2 domains	α1 and β1 domains
Binding site for T cell coreceptor	CD8 binds mainly to the α3 domain	CD4 binds to a pocket created by parts of α2 and β2 domains
Size of peptide-binding cleft	Accommodates peptides of 8-11 residues	Accommodates peptides of 10-30 residues or more
Nomenclature		
Human	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DQ, HLA-DP
Mouse	H-2K, H-2D, H-2L	I-A, I-E

AlloAntigen Recognition

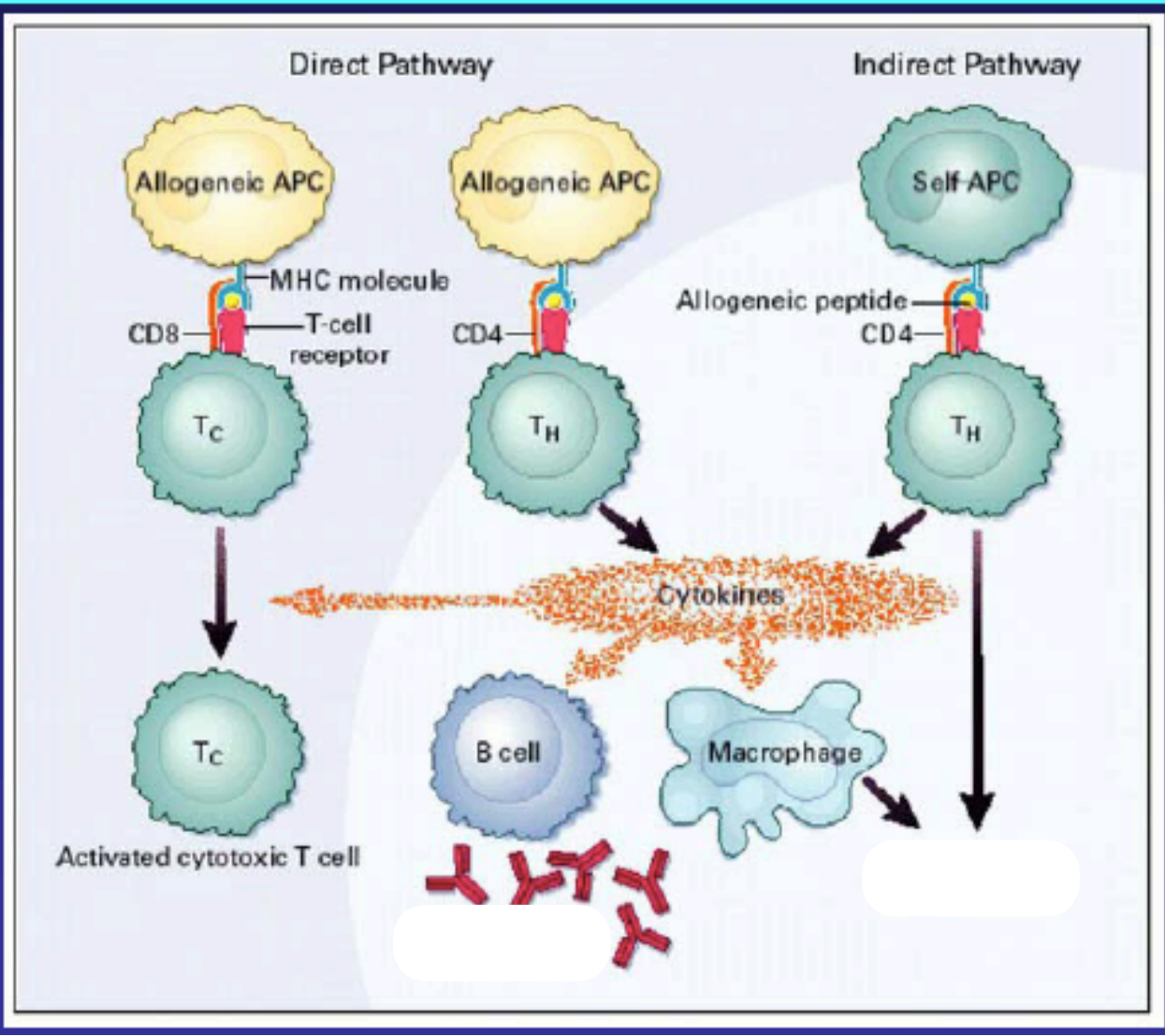
- Major Histocompatibility Complex (MHC)
  - Class I HLA A, B, C bind to TCR on CD8 T-Cell
  - Class II DR, DP, DQ bind to TCR on CD4 T-Cell
  - Most polymorphic genes in human genome
  - Co-dominantly expressed
- Direct presentation (Donor APC)
  - Unprocessed allogeneic MHC
- Indirect presentation (Host APC)
  - Processed peptide of allogeneic MHC



T cell recognizes unprocessed allogeneic MHC molecule on graft APC



Direct and Indirect AlloAntigen Recognition



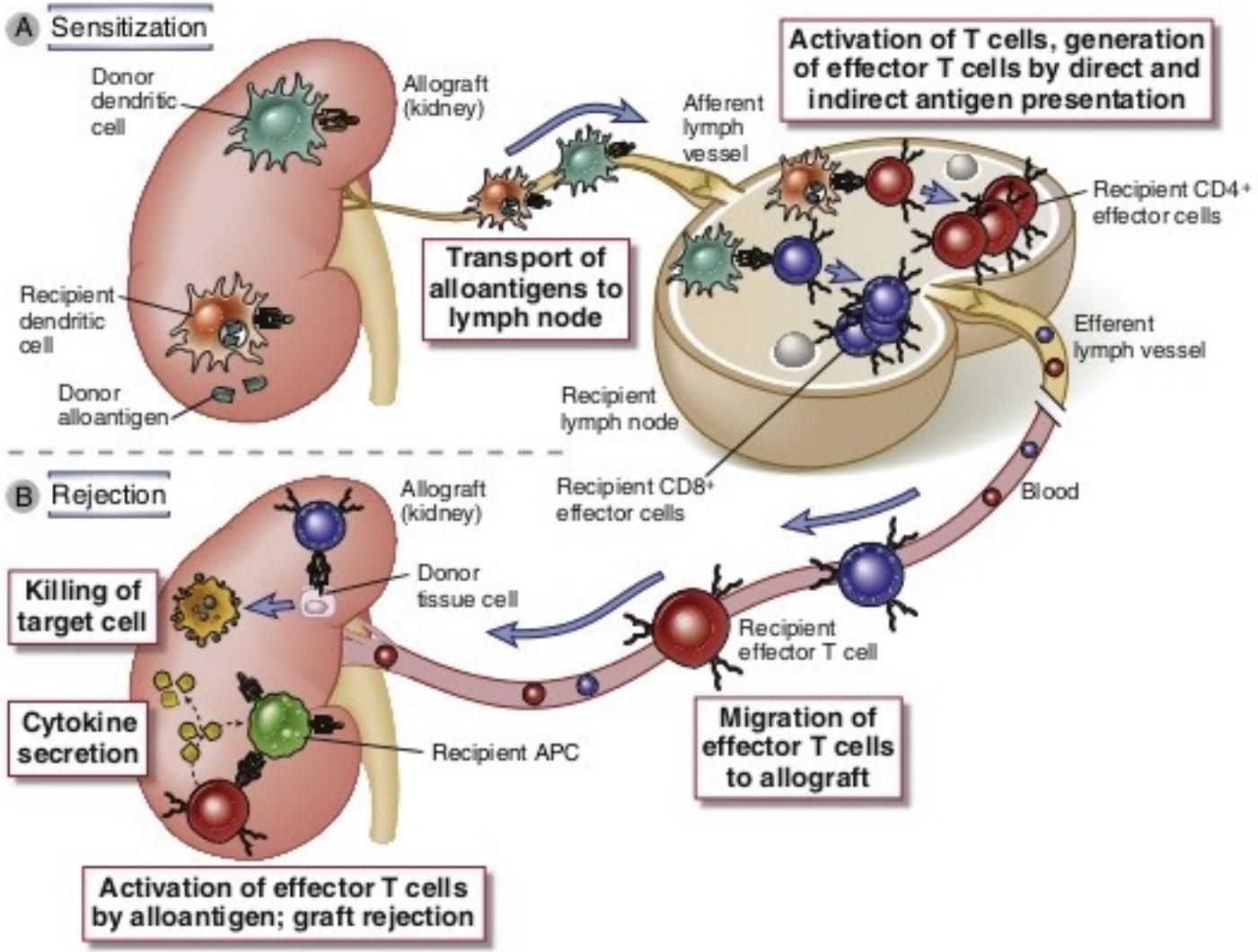
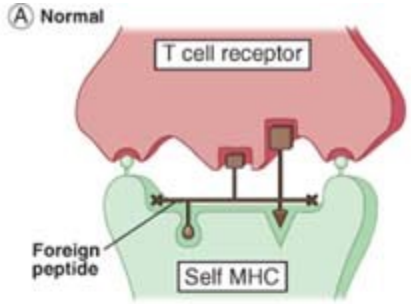


FIGURE 17-6 Activation of alloreactive T cells. A, In the case of direct allorecognition, donor dendritic cells in the allograft migrate to secondary lymphoid tissues, where they present allogeneic MHC molecules to host T cells. In the case of indirect allorecognition, recipient dendritic cells that have entered the allograft transport donor MHC proteins to secondary lymphoid tissues and present peptides derived from these MHC proteins to alloreactive host T cells. In both cases, the T cells become activated and differentiate into effector cells. **B,** The alloreactive effector T cells migrate into the allograft, become reactivated by alloantigen, and mediate damage.

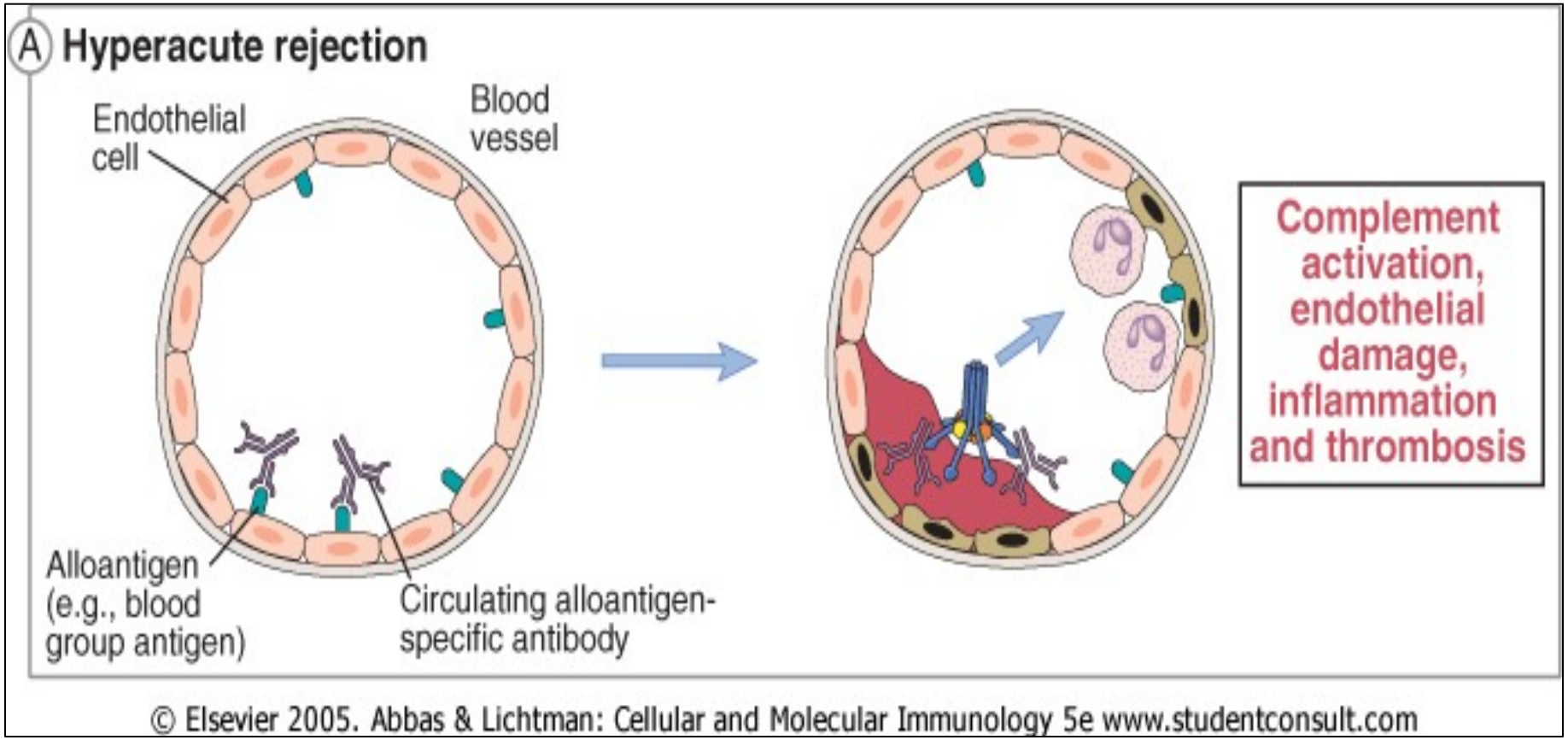


Self MHC molecule presents foreign peptide to T cell selected to recognize self MHC weakly, but may recognize self MHC–foreign peptide complexes well

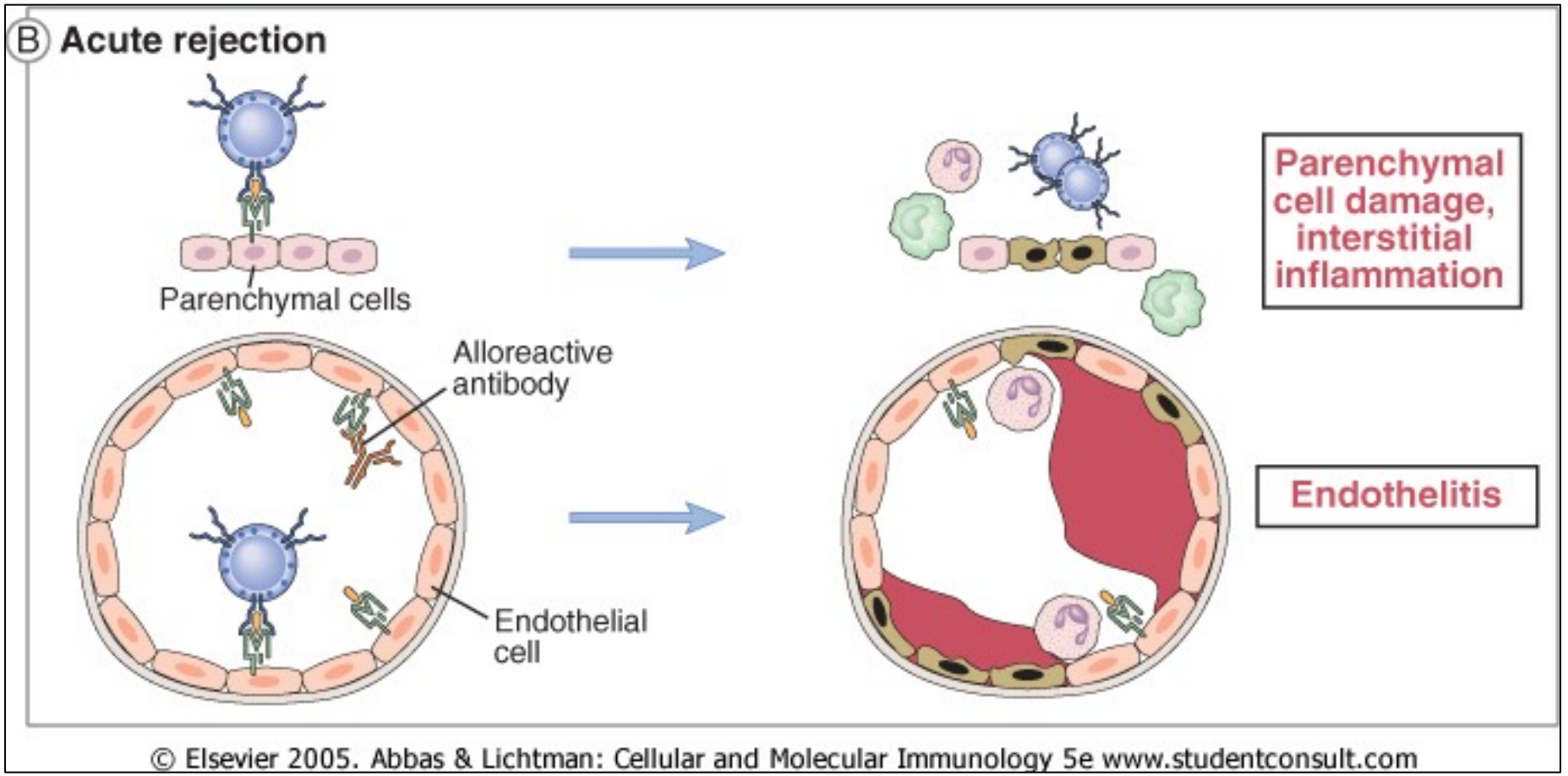
Hyperacute rejection

- In 24 h
- Cross-reactivity donor serum vs recipient cells
- Presence of anti-Class I MHC antibodies
- Worst prognosis (100 % loss of function)

Hyperacute rejection: immunological mechanism



Acute rejection: immunological mechanism



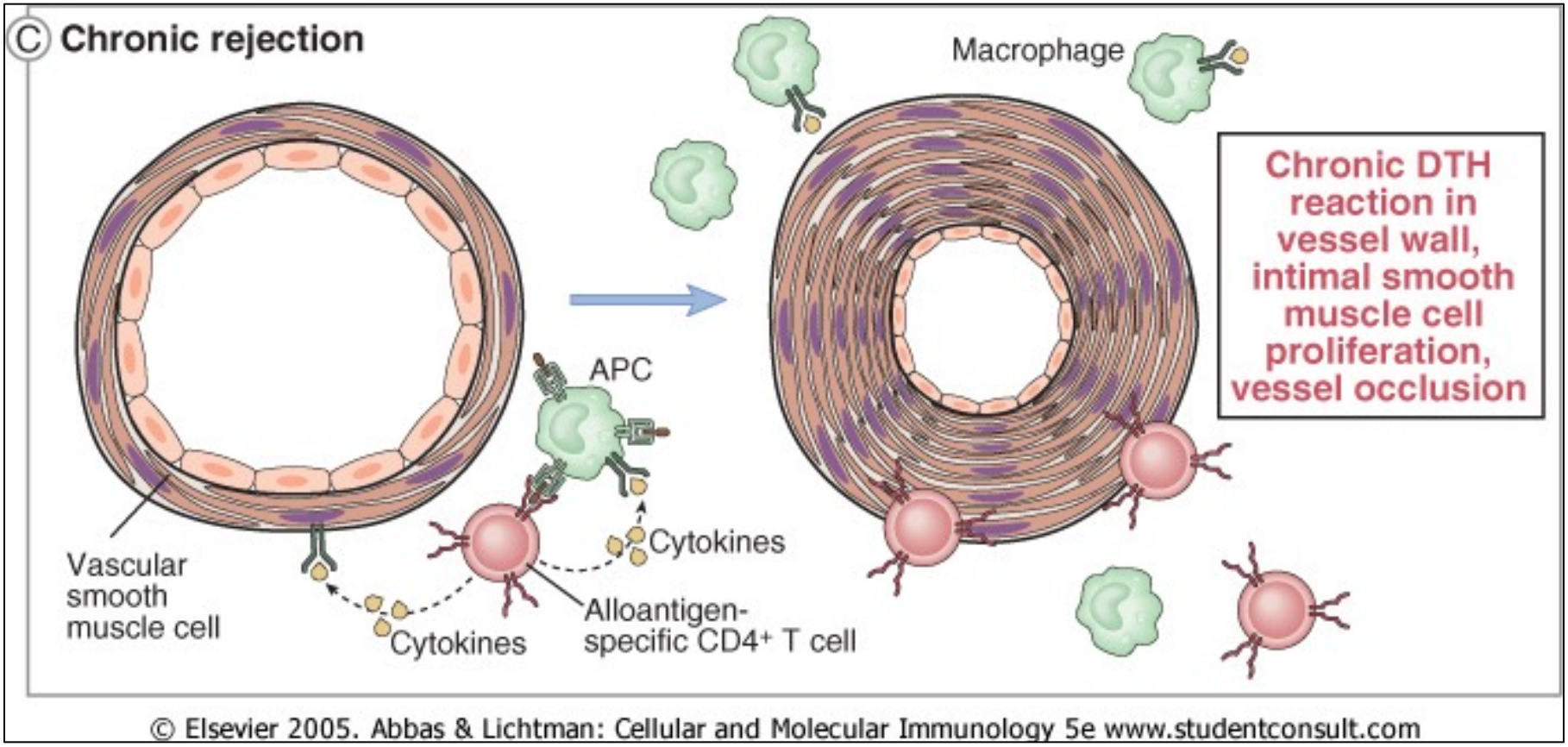
Mechanisms of cellular damages in acute rejection

A- Citokines produced by Macrophages and PMN

B- Specific T-cells produce TNF-α and perforine-granzyme

C- Bound antibodies induce CDC and ADCC

Chronic rejection: immunological mechanism



Chronic rejection in kidney

- After 60 gg
- Cell proliferation in intima, fibrosis and occlusion of vessels
- Hypertension
- atrofia (tubulo-interstitial)
- atrofia (glomerular)
- reduction of renal functionality

Pathological Mechanism of Rejection

Solid Organ

- Hyperacute
  - Minutes to hours
  - Preexisting antibodies (IgG)
  - Intravascular thrombosis
  - Hx of blood transfusion, transplantation or multiple pregnancies
- Acute Rejection
  - Few days to weeks
  - CD4 + CD8 T-Cells
  - Humoral antibody response
  - Parenchymal damage & Inflammation
- Chronic Rejection
  - Chronic fibrosis
  - Accelerated arteriosclerosis
  - 6 months to yrs
  - CD4, CD8, (Th2)
  - Macrophages

Bone Marrow/PBSC

Not Applicable

- Primary Graft Failure
  - 10 – 30 Days
  - Host NK Cells
  - Lysis of donor stem cells
- Secondary Graft Failure
  - 30 days – 6 months
  - Autologous T-Cells
    CD4 + CD8
  - Lysis of donor stem cells

Compatibility tests

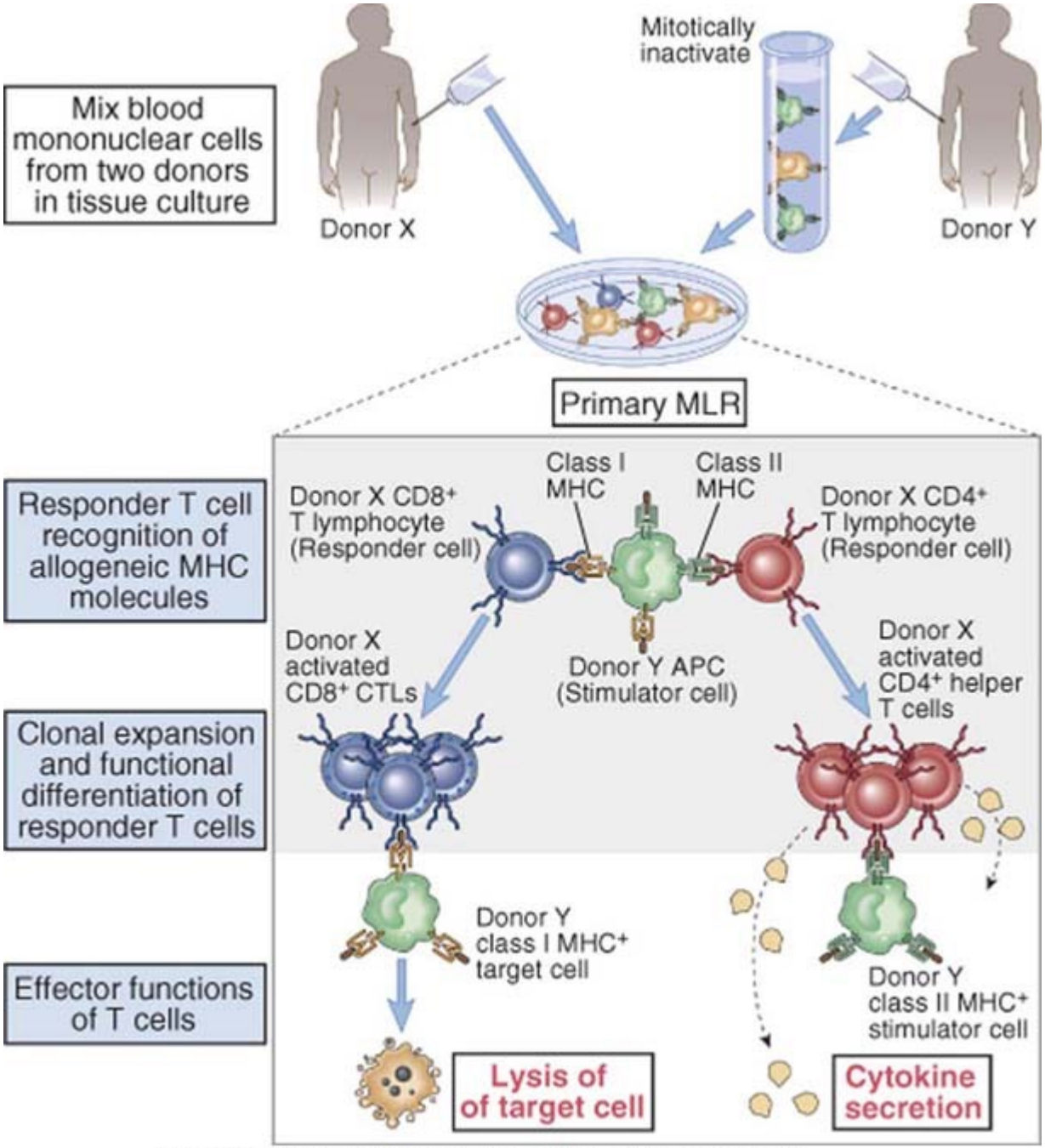
- **AB0 - Rh**
(IgM in AB0 system are the typical cause of hyper acute rejection)

- Tissue characterization: HLA
(mainly HLA-A, HLA-B, HLA-DR.
Study on lymphocytes, incubated with known Abs and a source of complement.
Evaluation of killed cells.
Now using PCR)

- Screening of preformed Abs
(donor serum + known HLA cells)

- **Crossmatching**
(donor serum + patient cells)

Mixed Lymphocytic Reaction



Transplantable organs

- Blood
- Kidney
- heart
- Lung
- Liver
- Bone marrow
- Placenta (Umbilical cord)
- Cornea

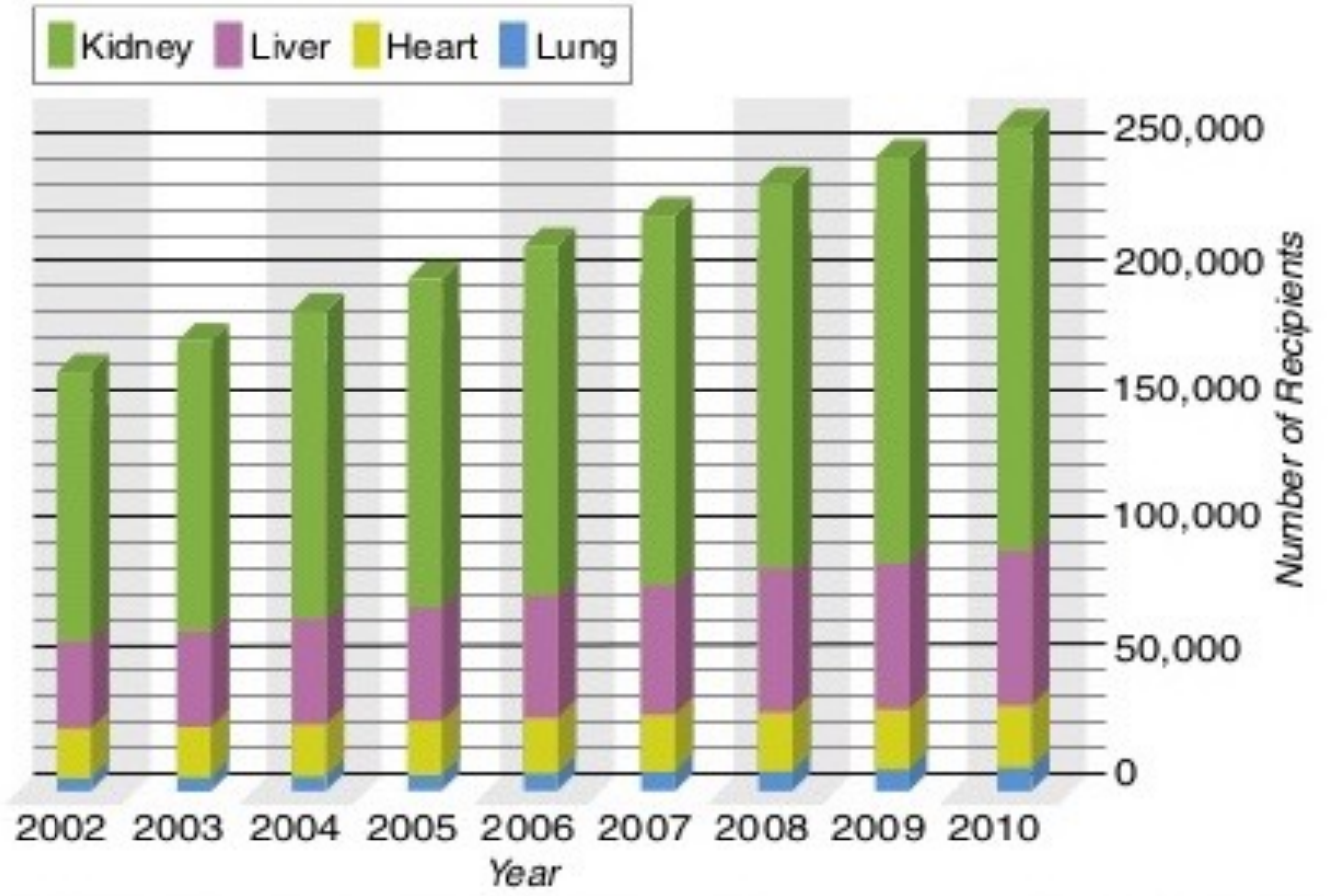


FIGURE 17-1 People in the United States living with functioning organ grafts, 2002-2010. (Data from SRTR annual report 2012. *Available at* http://www.srtr.org/. *Accessed April 2013.*)

Transplantation (Type)

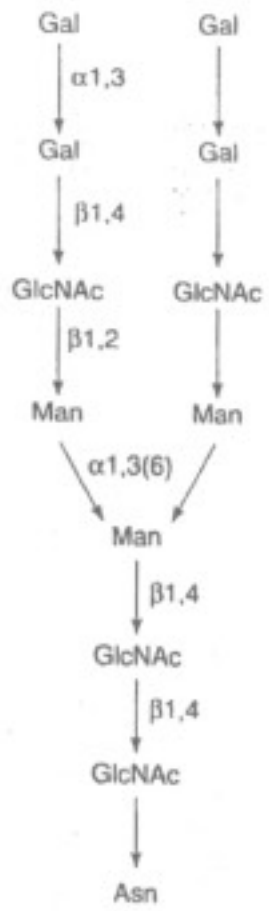
- Auto-transplantation

- Allo-transplantation

- Xeno-transplantation

xenotransplant

$$\underset{\text{Acceptor substrate}}{\text{Gal}\beta 1\text{–}4\text{GlcNAc–R}} + \underset{\text{uridine diphosphate–galactose}}{\text{UDP–Gal}} \xrightarrow{\alpha 1,3\text{GT}} \underset{\alpha\text{–gal epitope}}{\text{Gal}\alpha 1\text{–}3\text{Gal}\beta 1\text{–}4\text{GlcNAc–R}} + \text{UDP}$$



Blood transfusion

Blood

- Autotransplantation

- ABO system ed Rh system
- HLA system

Plasma

- Autotransplantation

-ABO system ed Rh system

Bone marrow transplantation

-…… to allow hematopoietic stem cell transplantation

- patient stimulation with GM-CSF to increase cell recovery

- treatment of diseases of the hematopoietic and immune system

- to collect stem cells to induce their differentiation in specific cells (treatment of diseases in other organs)

Procedure in solid organ transplantation

1. transplantation request
2. patient treatment waiting for the transplantation
3. compatibility tests
4. organ explant
5. organ transportation
6. organ transplantation
7. evaluation of the function
8. evaluation of the reject

Fetal immune response

No immune response to the fetus.

- absence of classic MHC

- privileged microenvironment from an immunological point of vie, like CNS, eye, testis (high concentration of immunosuppressive cytokines - like TGF-β - and resident Treg lymphocytes)

Metodi di immunosopressione usati in clinica

Farmaco	Meccanismo d'azione
Ciclosporina e FK-506	Blocca la produzione di citochine da parte dei linfociti T inibendo il fattore NF-AT
Azatioprina	Blocca la proliferazione dei precursori dei linfociti
Mofetil-micofenolato	Blocca la proliferazione dei linfociti inibendo la sintesi di guanina
Rapamicina	Blocca la proloferazione linfocitaria inibendo la trasduzione del segnale dell'IL2
Corticosteroidi	Riducono l'infiammazione inibendo la secrezione di citochine da parte dei macrofagi
Ab anti-CD3	Elimina i linfociti T promuovendo fagocitosi e attivazione del complemento
Ab anti-recettore dell'IL2	Inibisce la proliferazione dei linfociti T bloccando il legame di IL2
CTLA-4-Ig	Inibisce l'attivazione die linfociti T il legame della molecola costimolatrice B7 (APC) al CD28 (linfociti T)
Ab anti-CD40 ligando	Inibisce l'attivazione dei macrofagi e dell'endotelio bloccando l'interazione il legame CD40L (linfociti T) al CD40 (macrofagi)

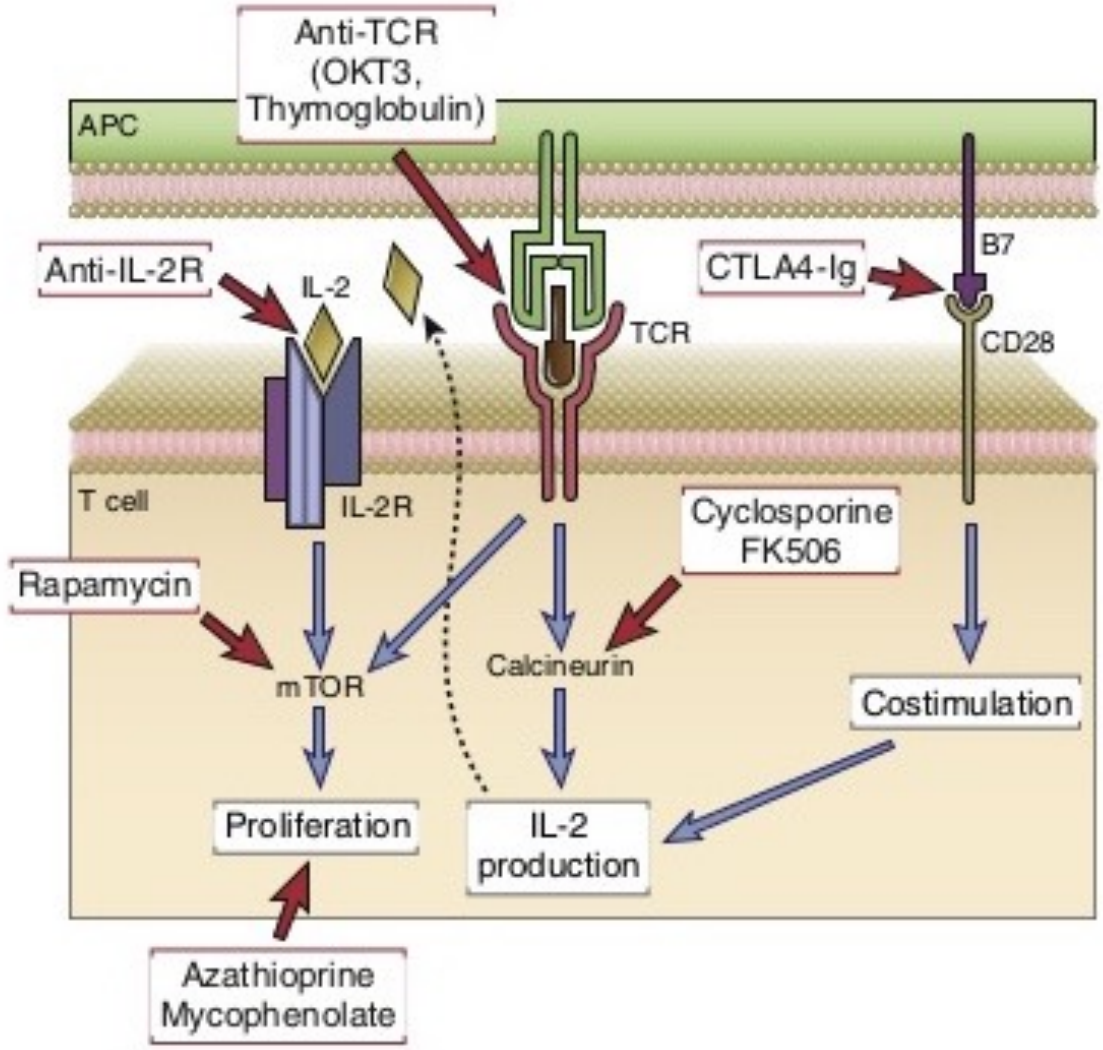
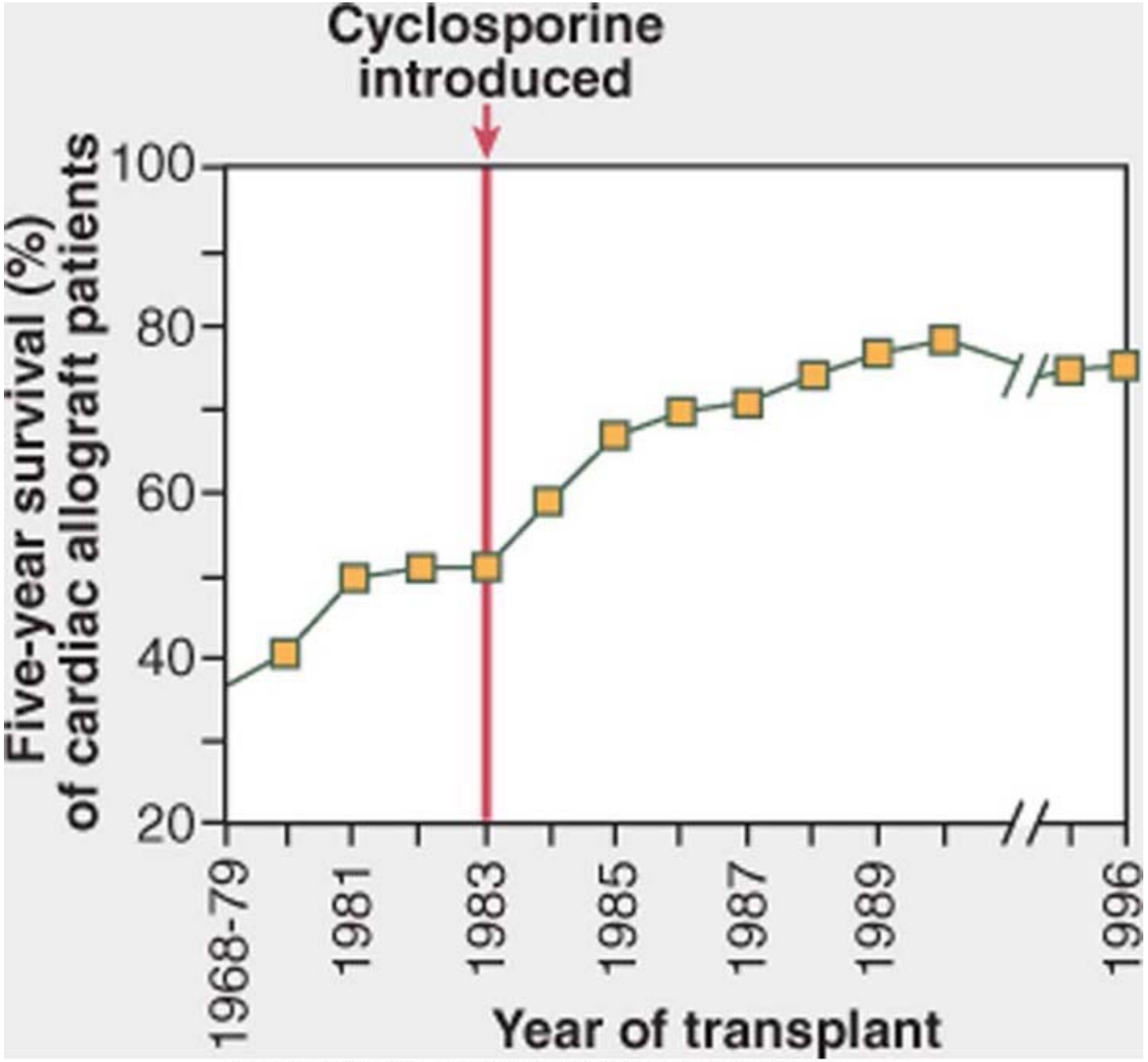


FIGURE 17-11 Mechanisms of action of immunosuppressive drugs. Each major category of drugs used to prevent or to treat allograft rejection is shown along with the molecular targets of the drugs.



Infezioni potenzialmente trasmissibili dall'organo trapiantato

- CMV (sangue, polmoni, cuore, cute, fegato, cervello)
- EBV (idem)
- HHV8 (Kaposi)
- HBV / HCV (fegato)
- Candida (sangue, polmone, fegato, cute)
- Toxoplasma (polmone, cuore, cervello)
- Strongiloides

Rischio di tumori nel trapiantato (rene)

- L'incidenza è del 5-6 % (100 volte quella della popolazione generale)

- Sedi:
  - cute
  - labbra
  - collo dell'utero
  - linfomi NH

Infezioni precoci (< 1 mese) dopo trapianto di rene

- Vie urinarie:
  - batteri : E.coli, Klebsiella, Pseudomonas, Enterococco spesso con batteriemia
  - Candida

- Polmone:
  - batteri (Legionella)

Profilaxis – before transplantation

- Metilprednisolone (250 mg il giorno prima ; a scalare fino a 10-15 mg/die; 1 g in pulse dose x 3 gg nell'acuto)
- Micofenolato mofetil (azatioprina)
- Ciclosporina-A
- Tacrolimus
- Siero anti-linfocitario (anti-CD3) nell'acuto