Transplantation Immunology

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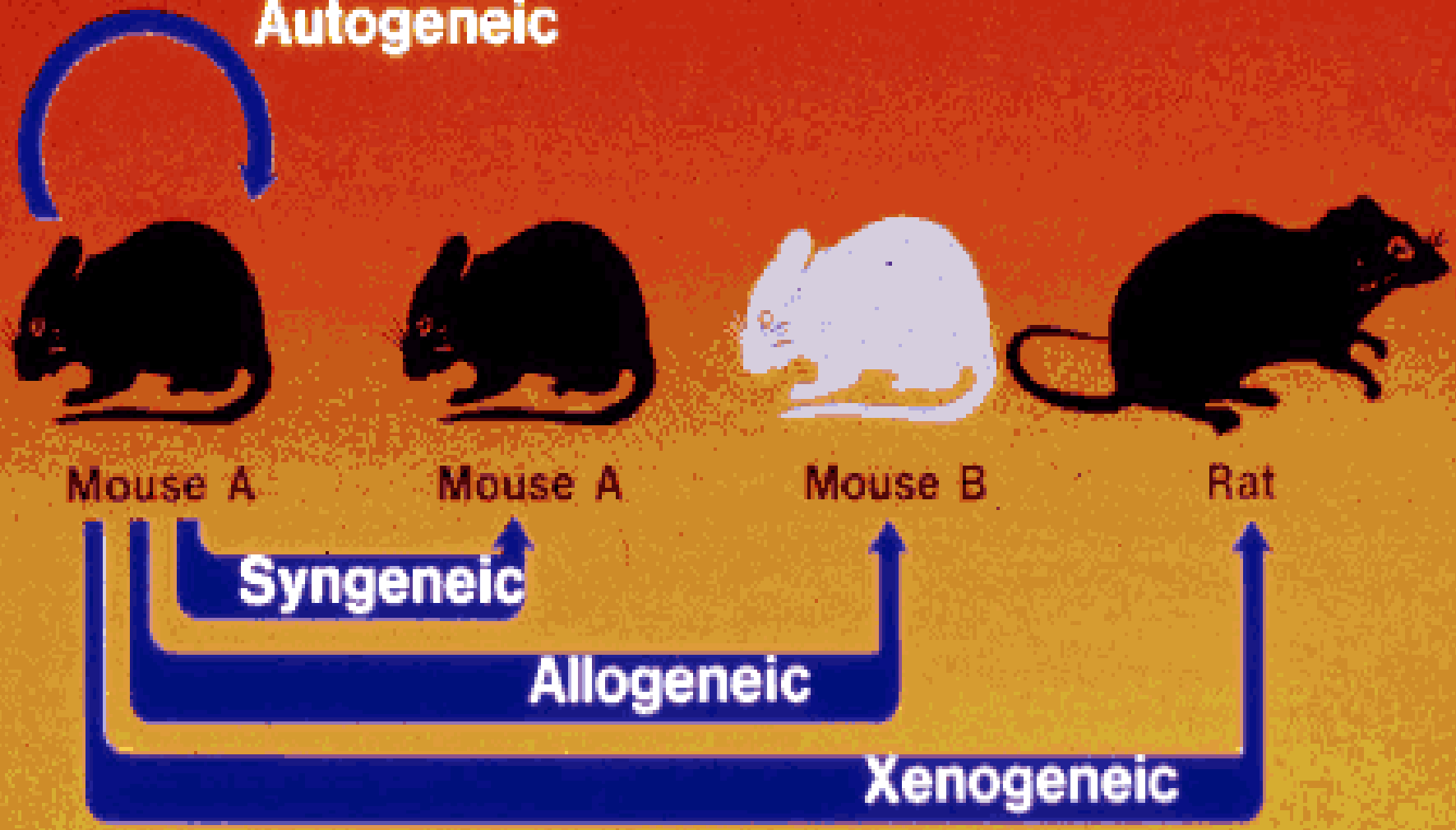
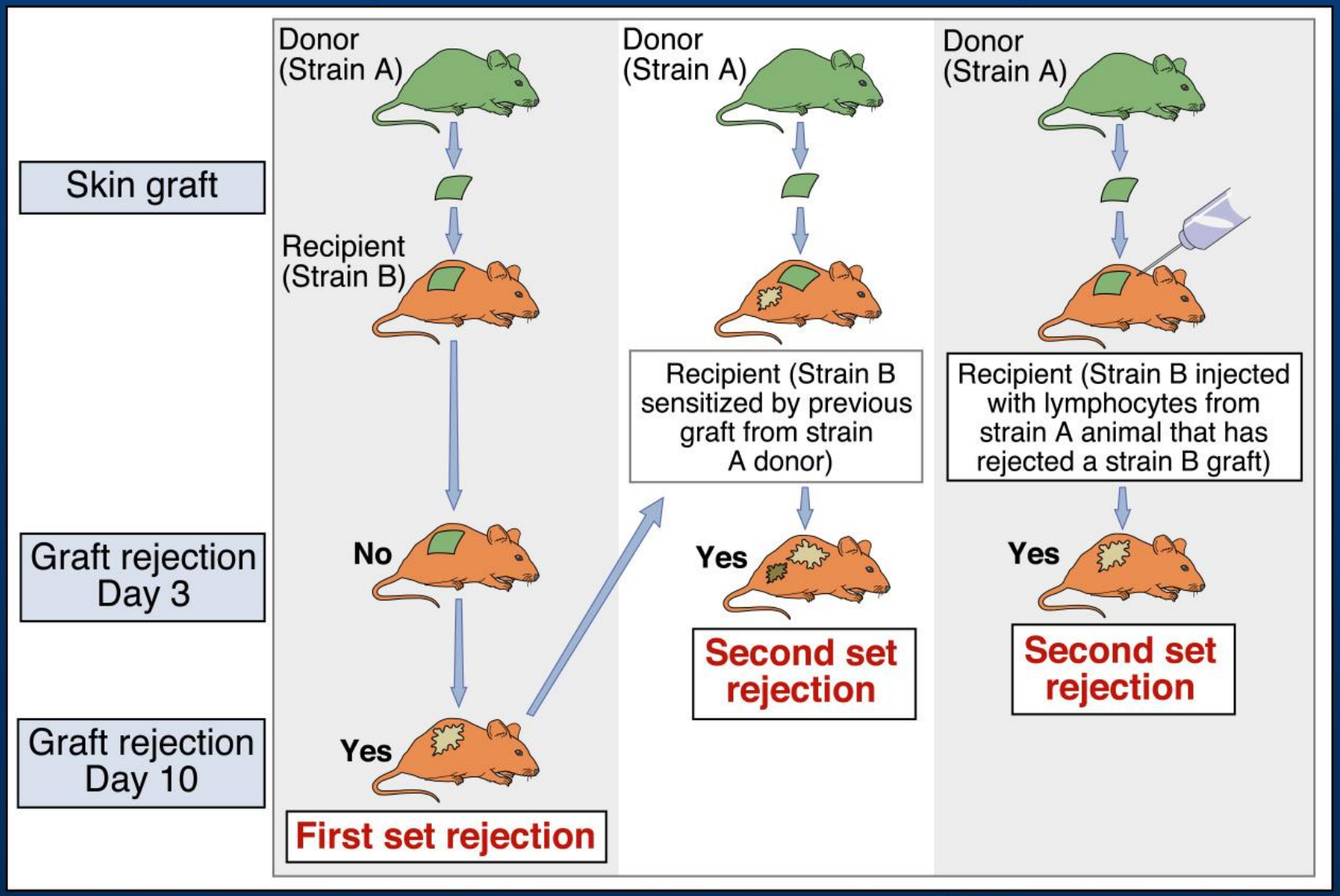
Transplantation, as the term used in immunology, refers to the act of transferring cells, tissues, or organs from one site to another. The desire to accomplish transplants stems from the realization that many diseases can be cured by implantation of a healthy organ, tissue, or cells (a graft) from one individual (the donor) to another in need of the transplant (the recipient or host). The development of surgical techniques that allow the facile reimplantation of organs has removed one barrier to successful transplantation, but others remain……

Tissue Graft Relationships And Terminology

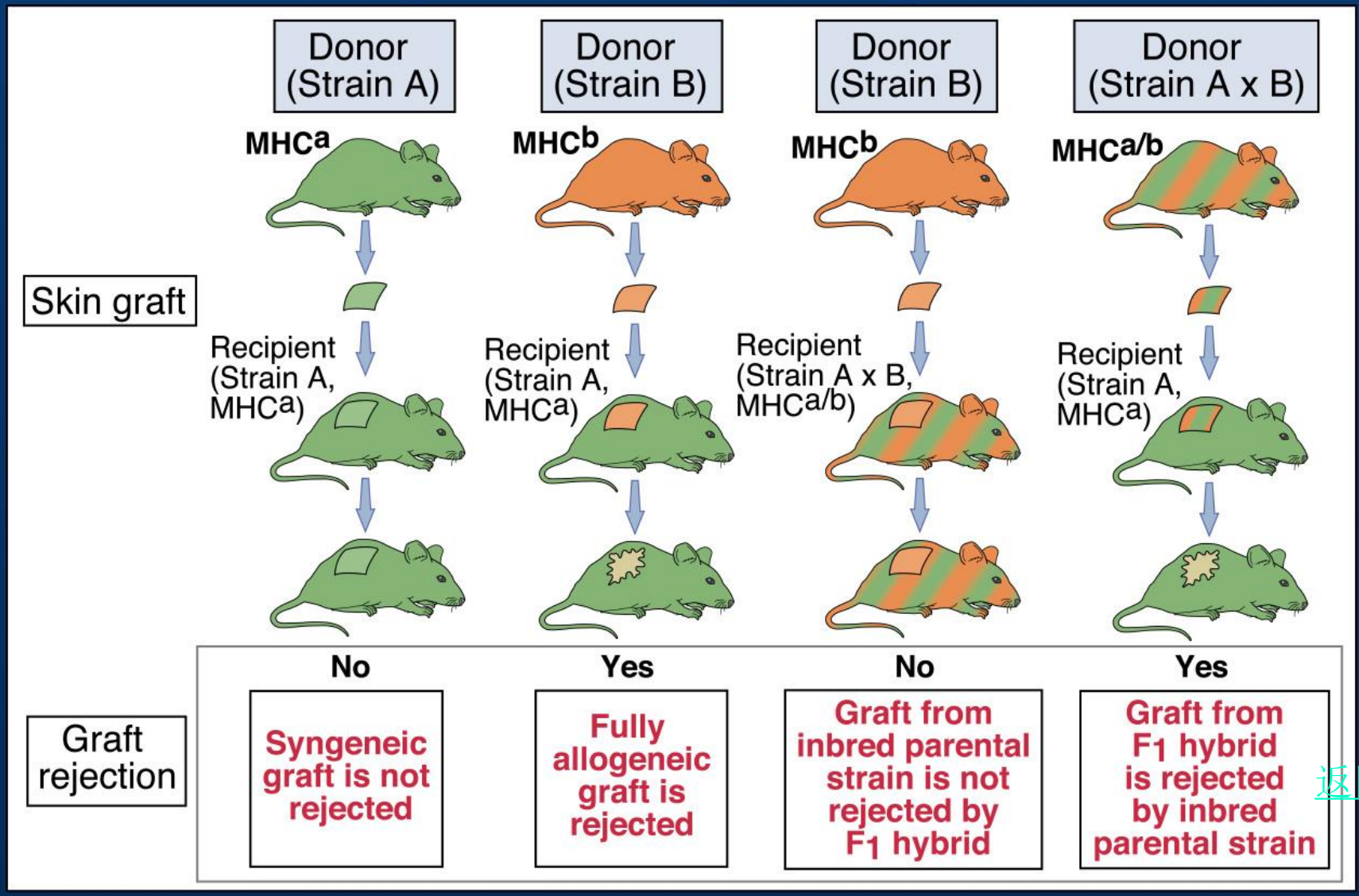


Graft rejection is an immune response



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-1

The genetics of graft rejection



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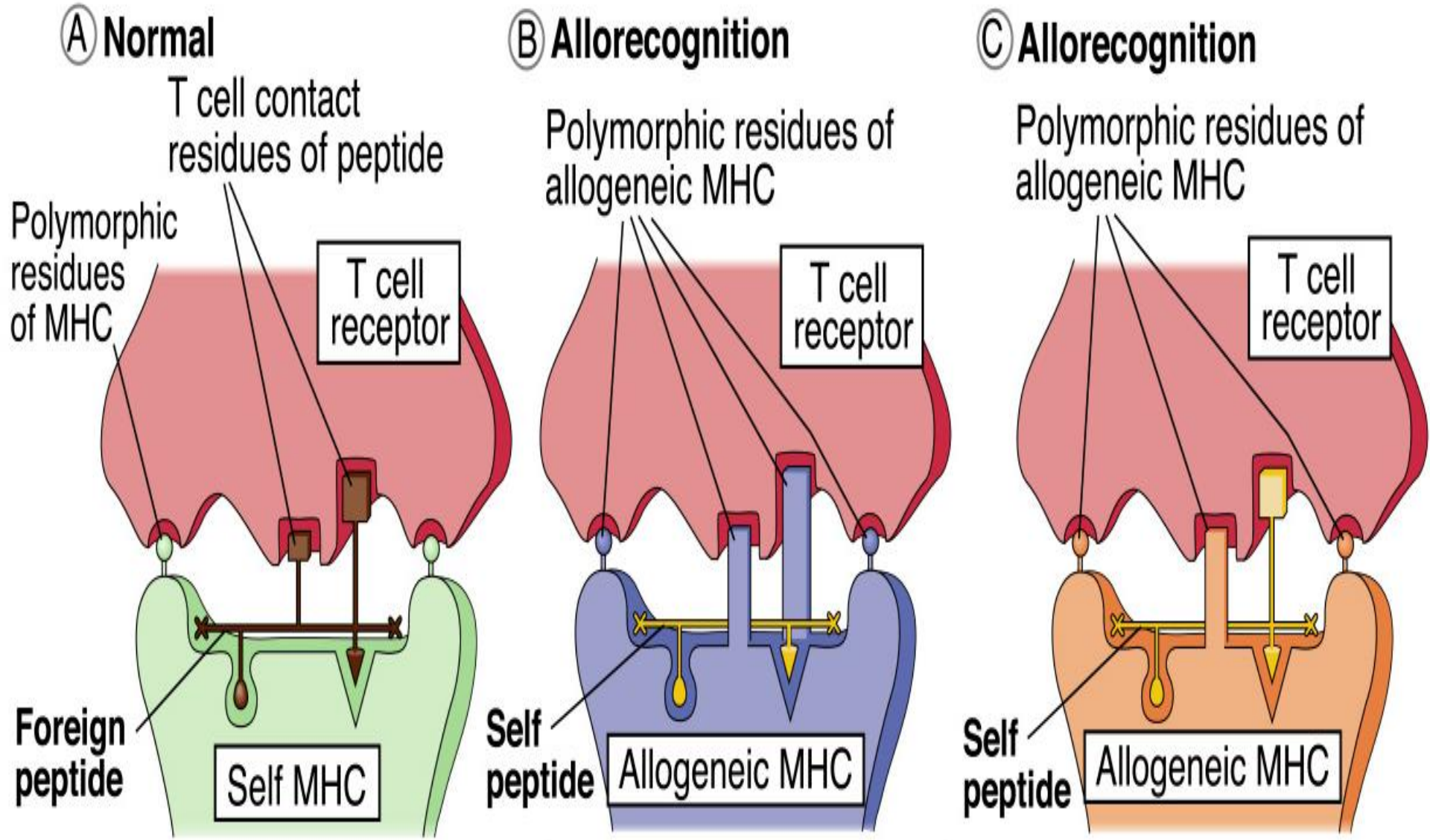
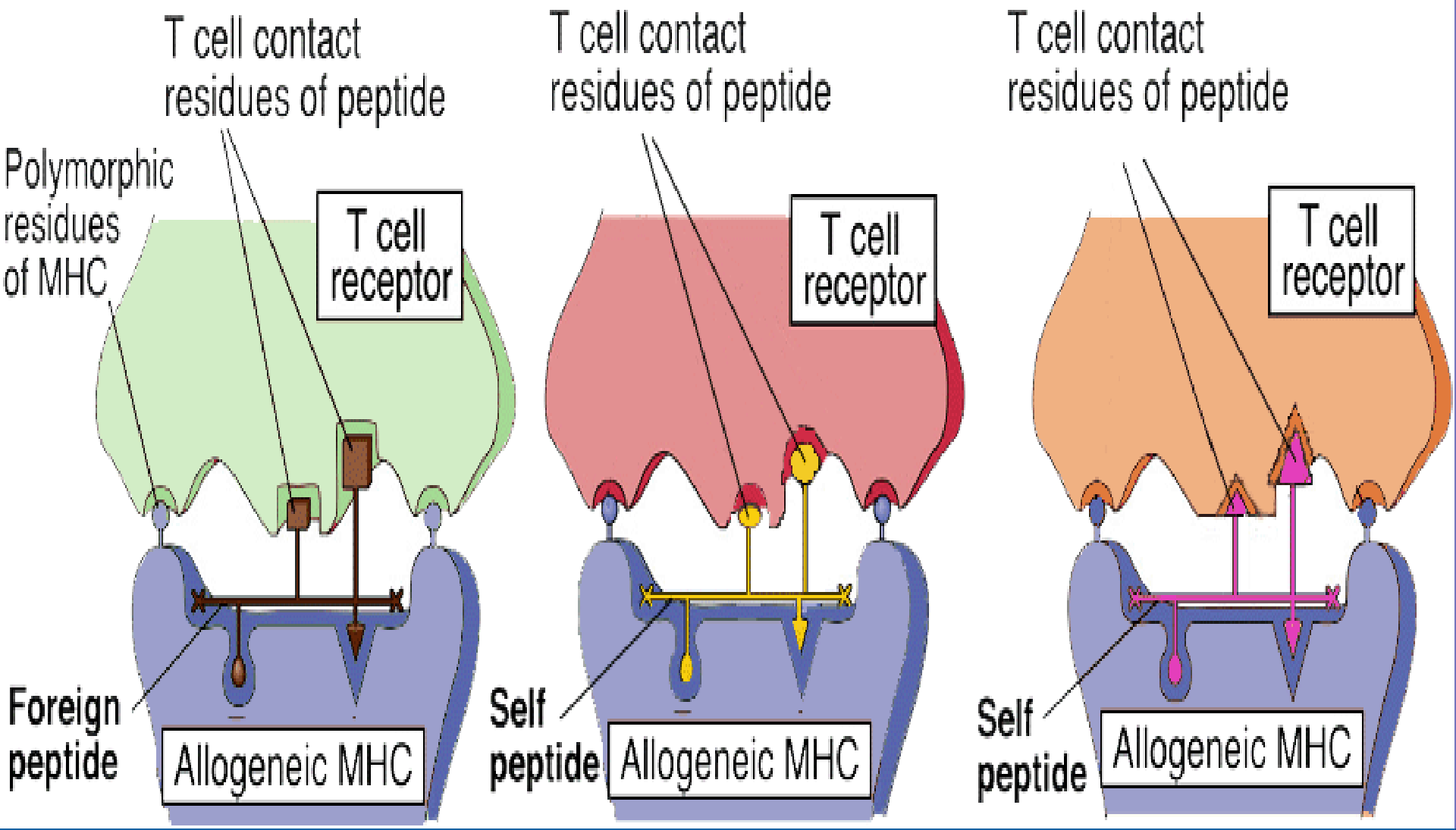
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-2



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig16-4

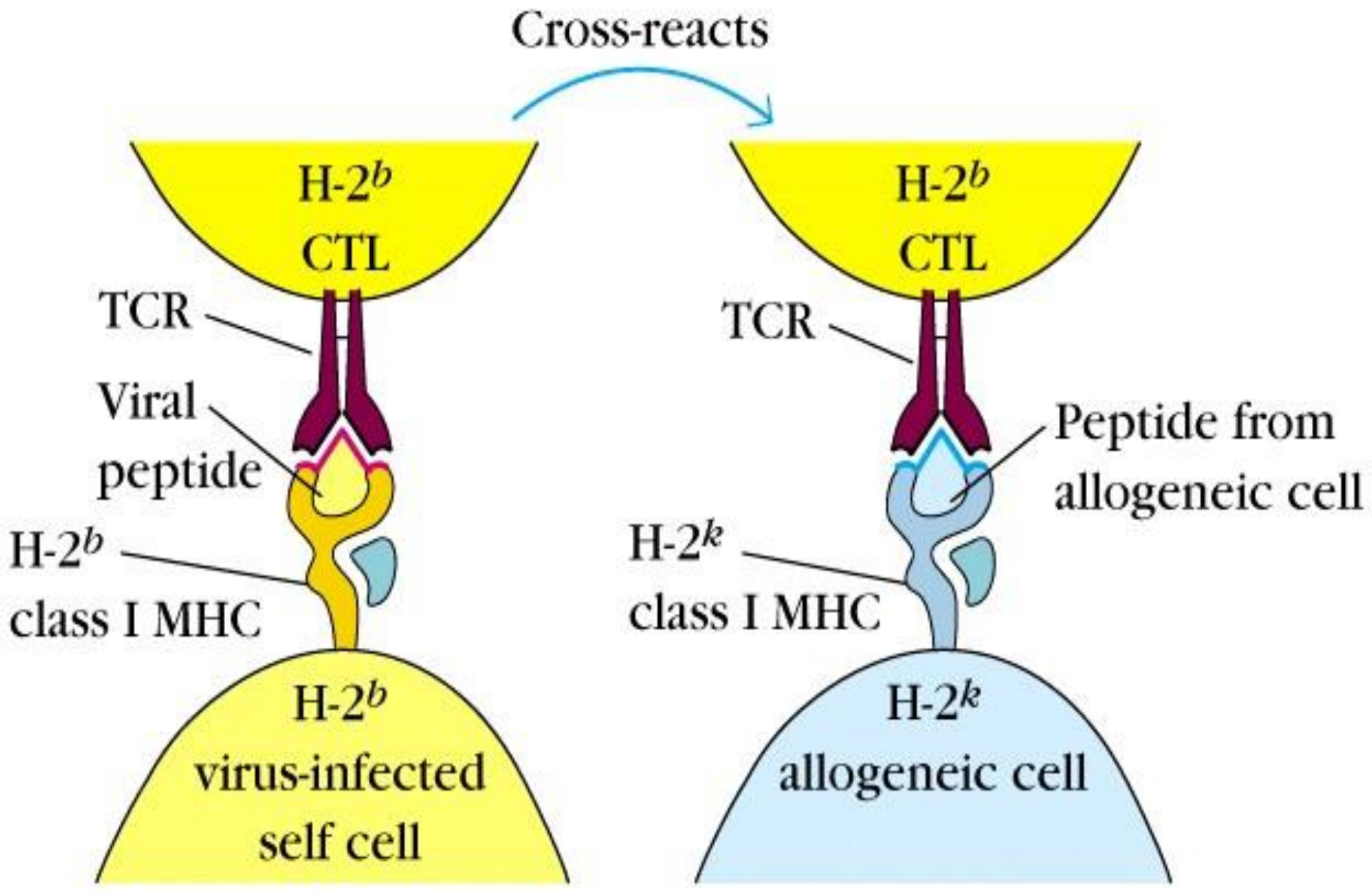
Direct recognition: degeneracy

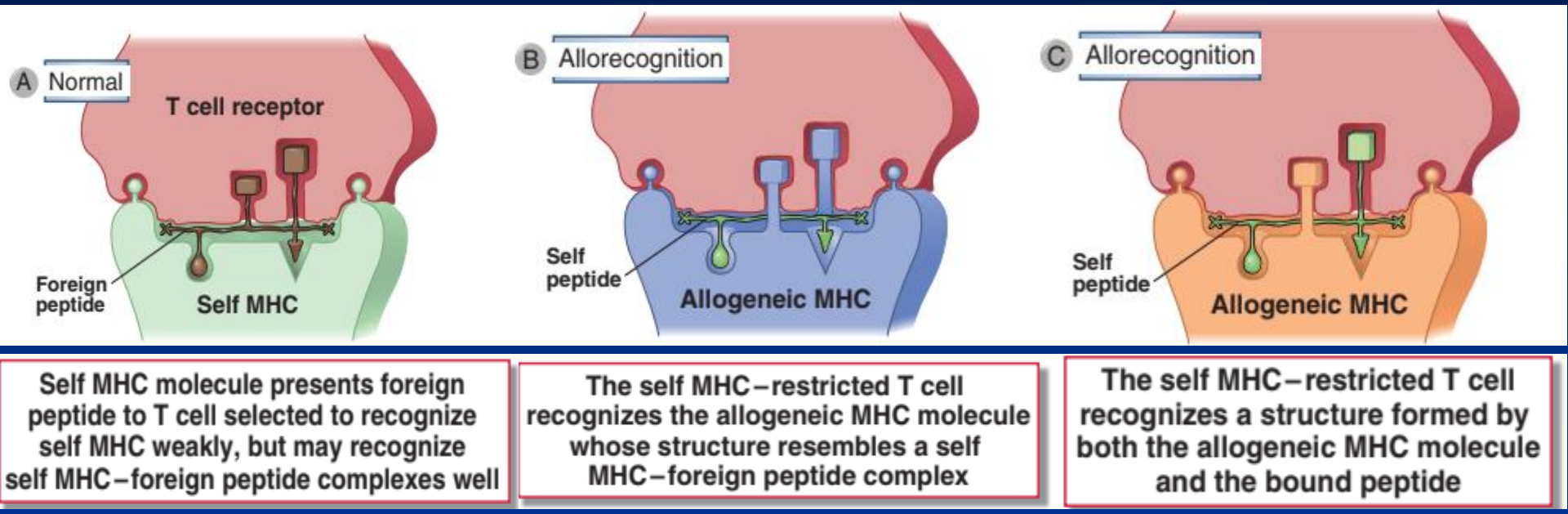


Direct recognition: flexibility

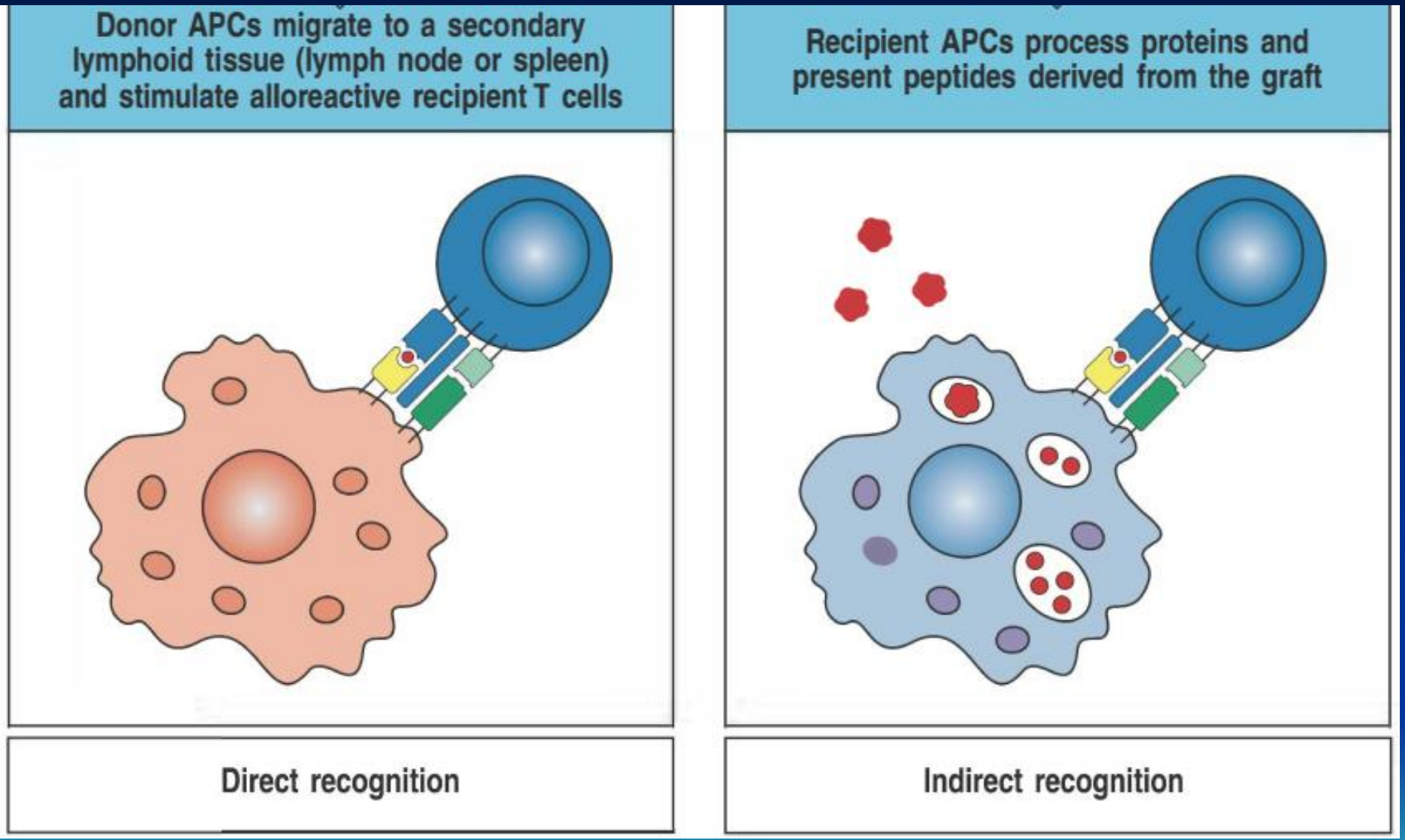
A Single Peptide-MHC Complex Positively Selects a Diverse and Specific CD8 T Cell Repertoire. Wang B, et al. **Science 2009; 326:871-874**

Alloreactivity





Molecular basis of direct recognition of allogeneic MHC molecules. Direct recognition of allogeneic MHC molecules may be thought of as a cross-reaction in which a T cell specific for a self MHC molecule–foreign peptide complex **(A)** also recognizes an allogeneic MHC molecule **(B, C)**. Nonpolymorphic donor peptides, labeled "self peptide," may not contribute to allorecognition **(B)** or they may **(C)**.



Alloantigens in grafted organs are recognized in two different ways.

Autografting

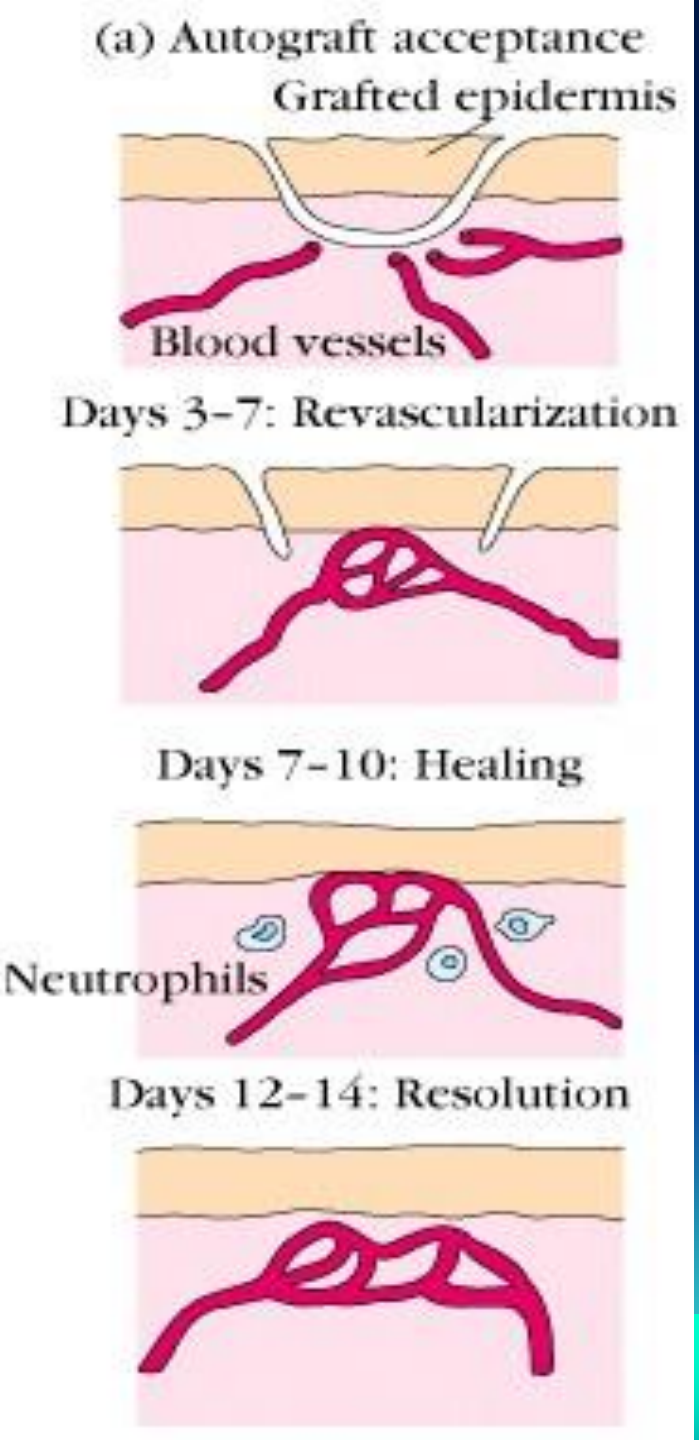
An example of graft acceptance

- The transfer of self tissue from one body site to another in the same individual

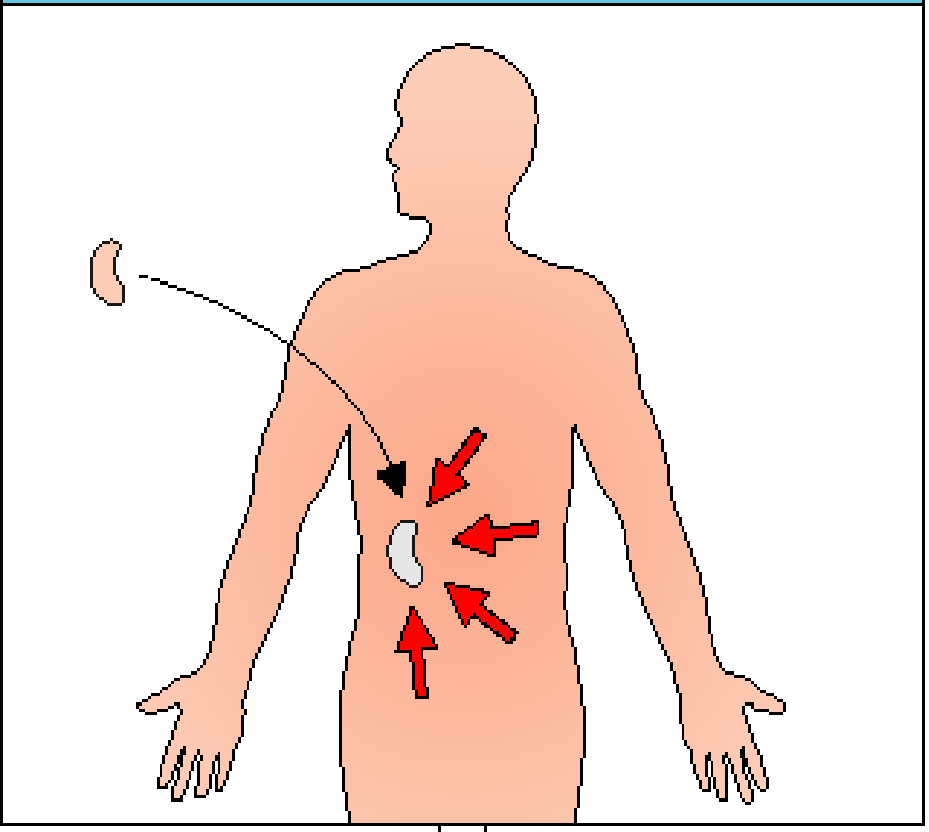
- Due to the genetic homology of the tissue, the immune system does not respond to it

Many uses:

- Skin grafts
- Bone marrow transplantation
- Stem cell transplantation
- Synthetic implantation

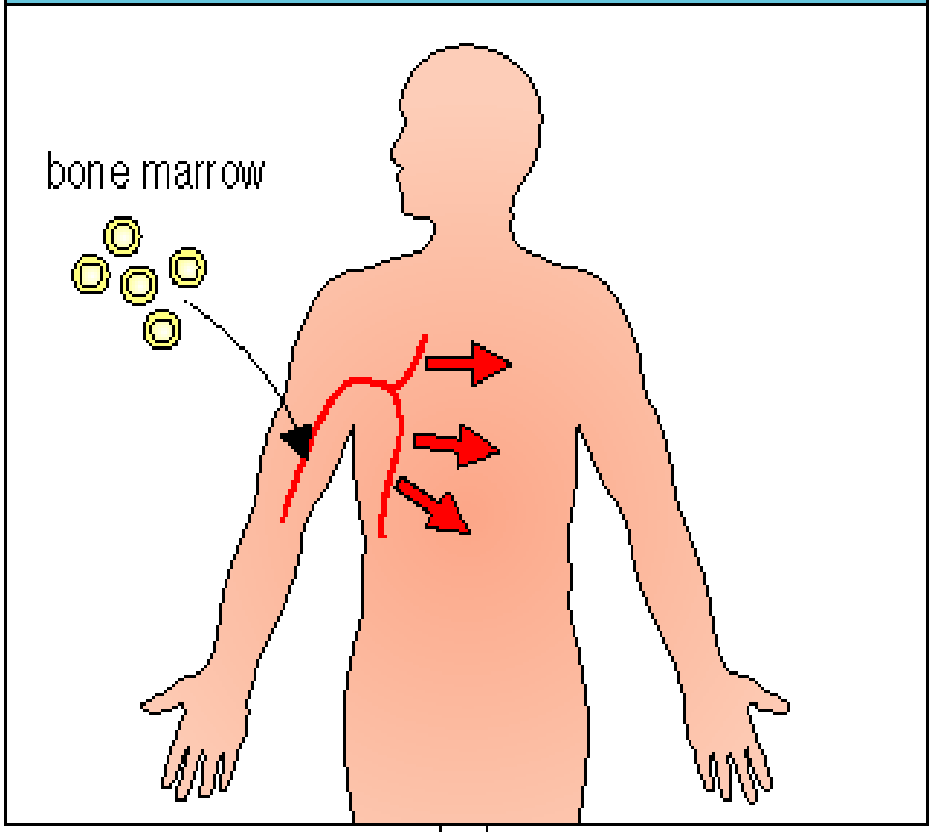


When a kidney is transplanted the recipient's T cells attack the transplant

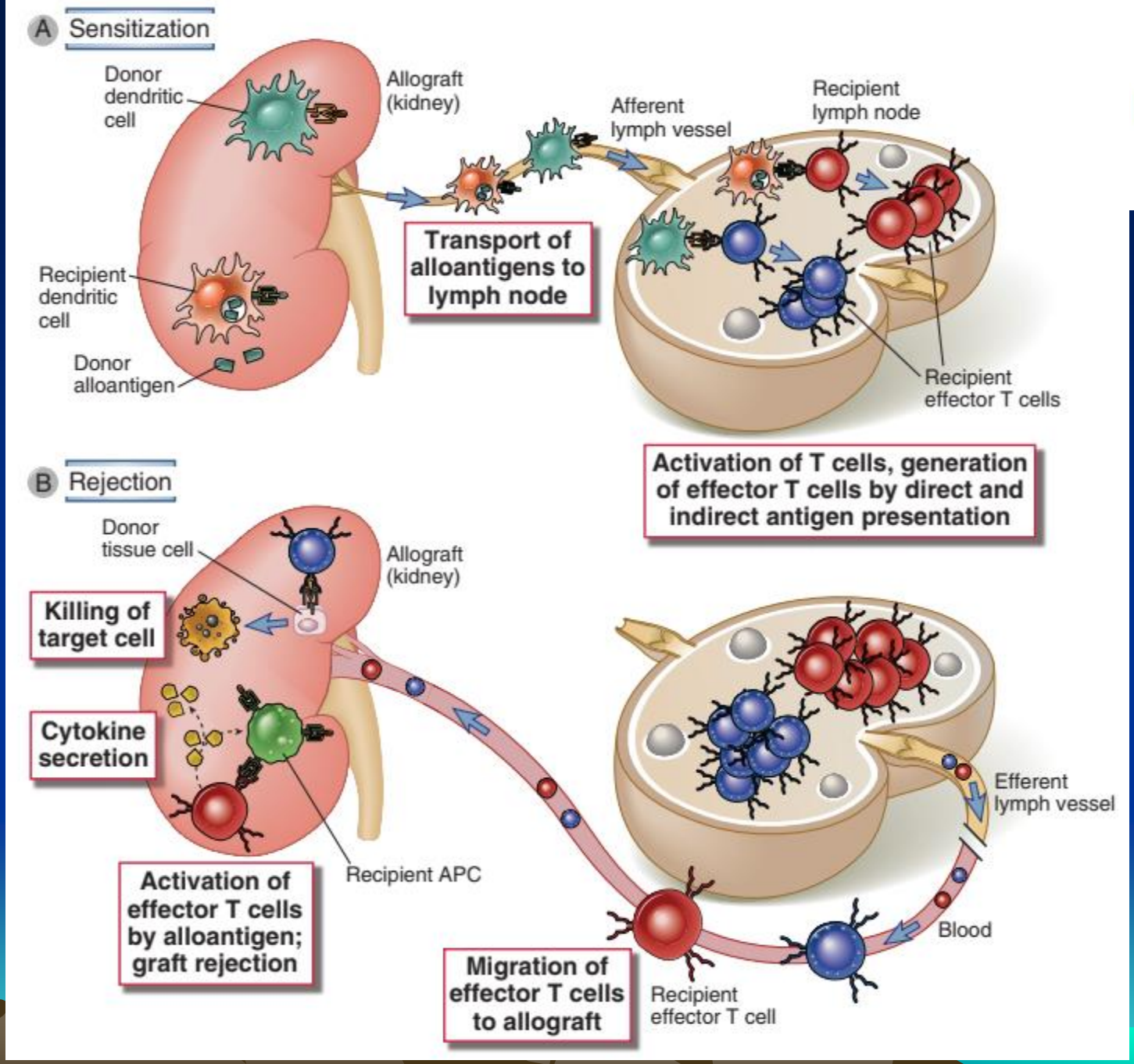


Transplant rejection (HVGR)

When bone marrow is transplanted the T cells in the transplant attack the recipient's tissues

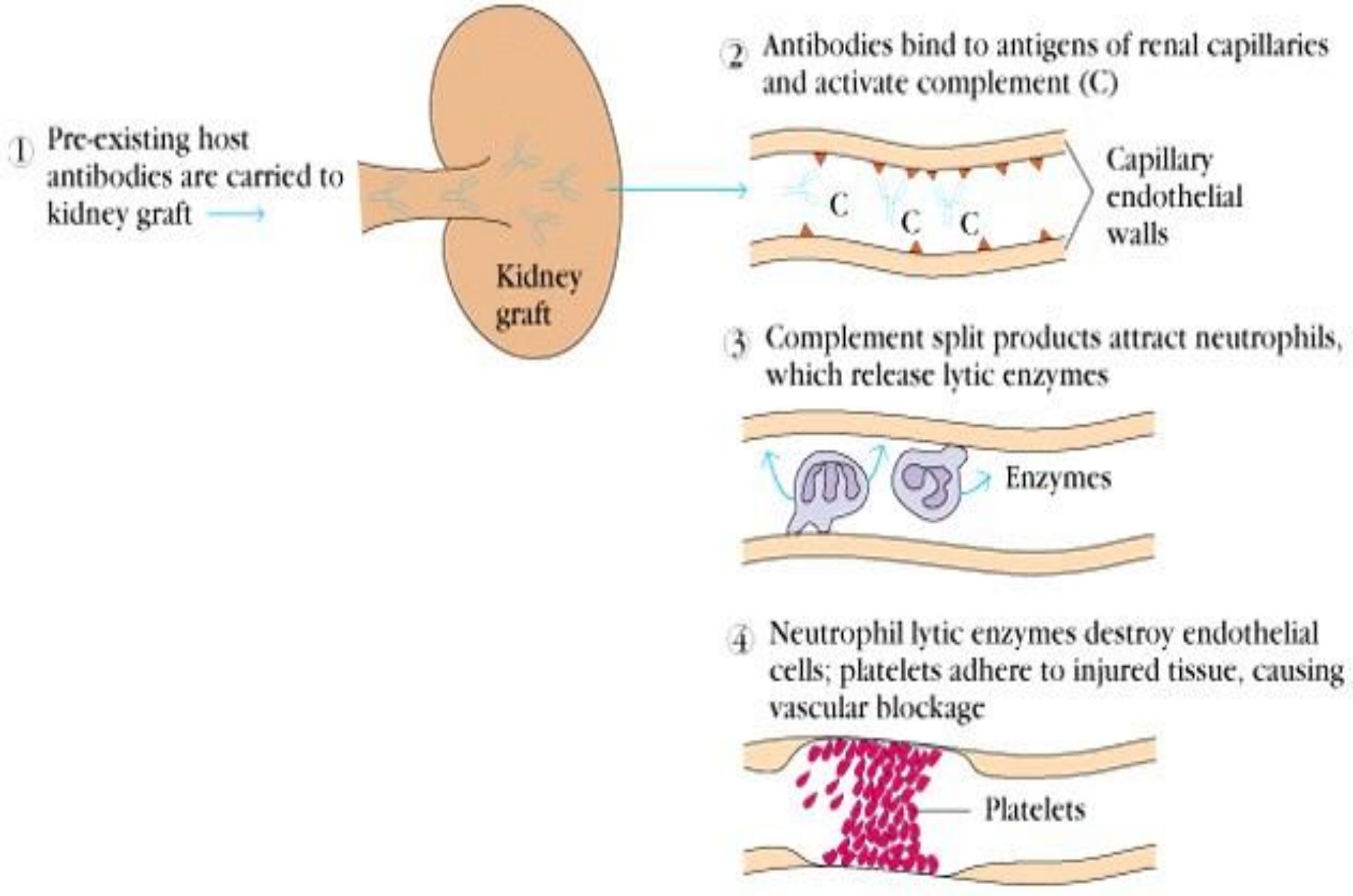


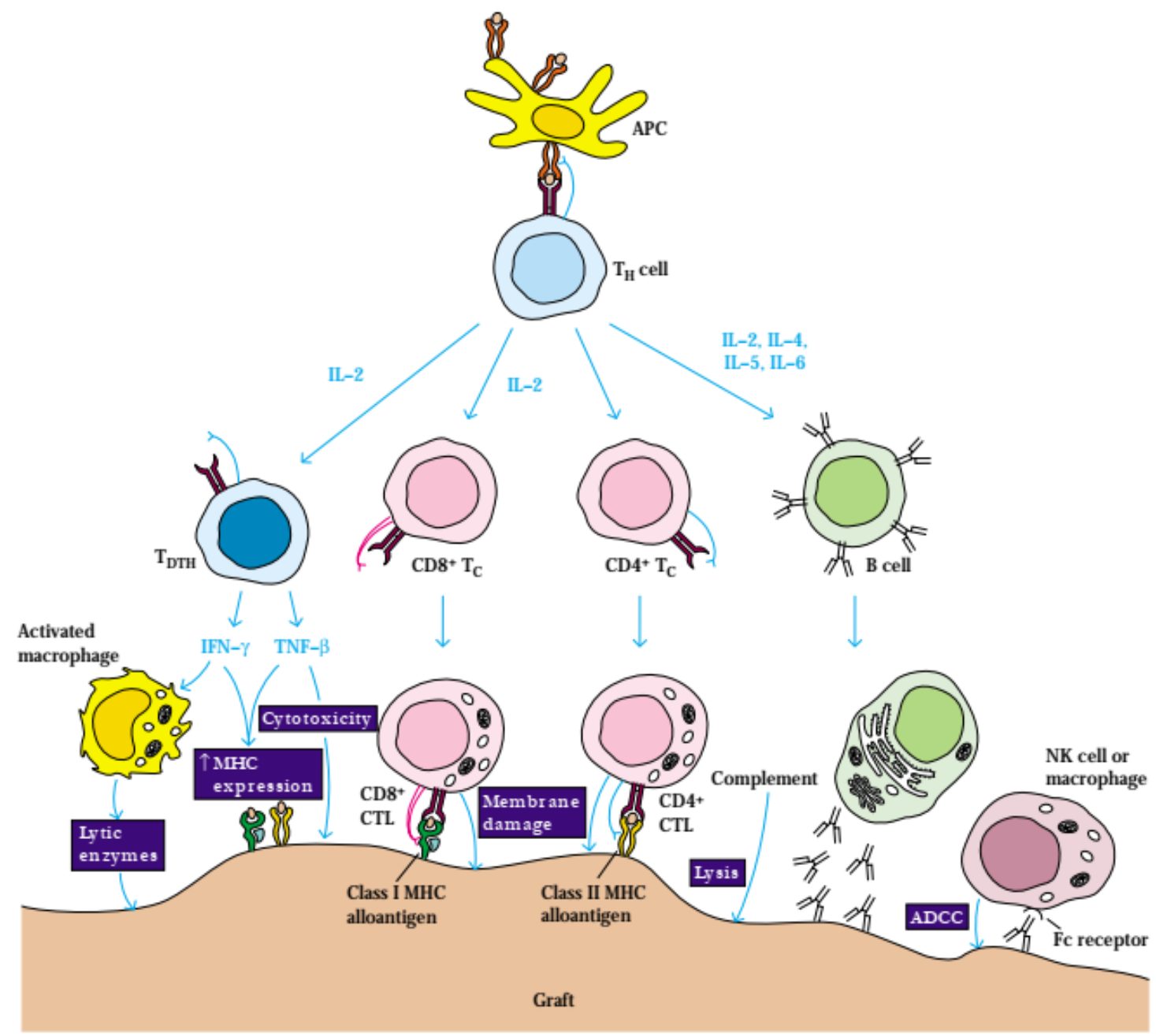
Graft-versus-host disease (GVHD)



Activation of alloreactive T cells

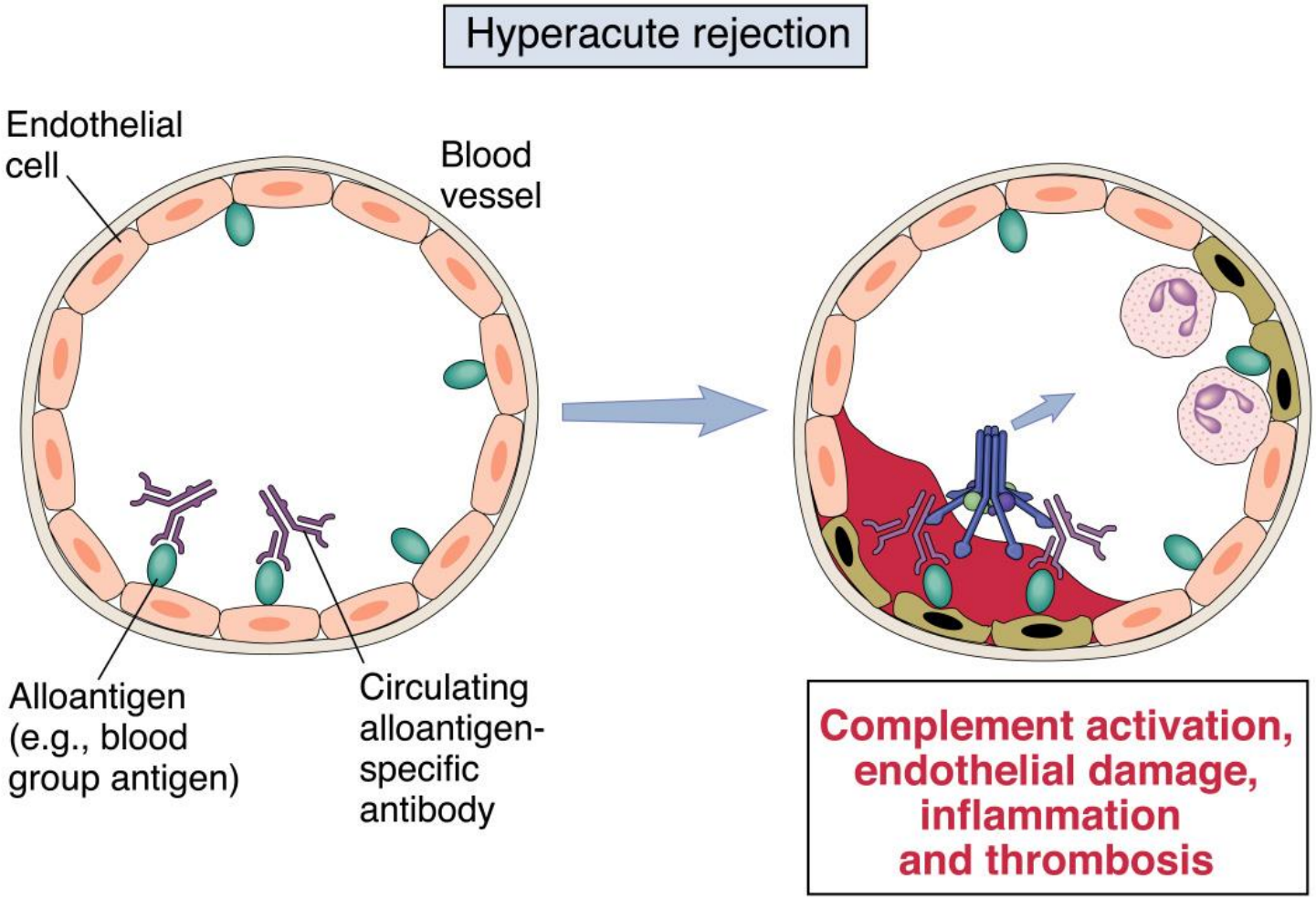
Hyperacute Rejection





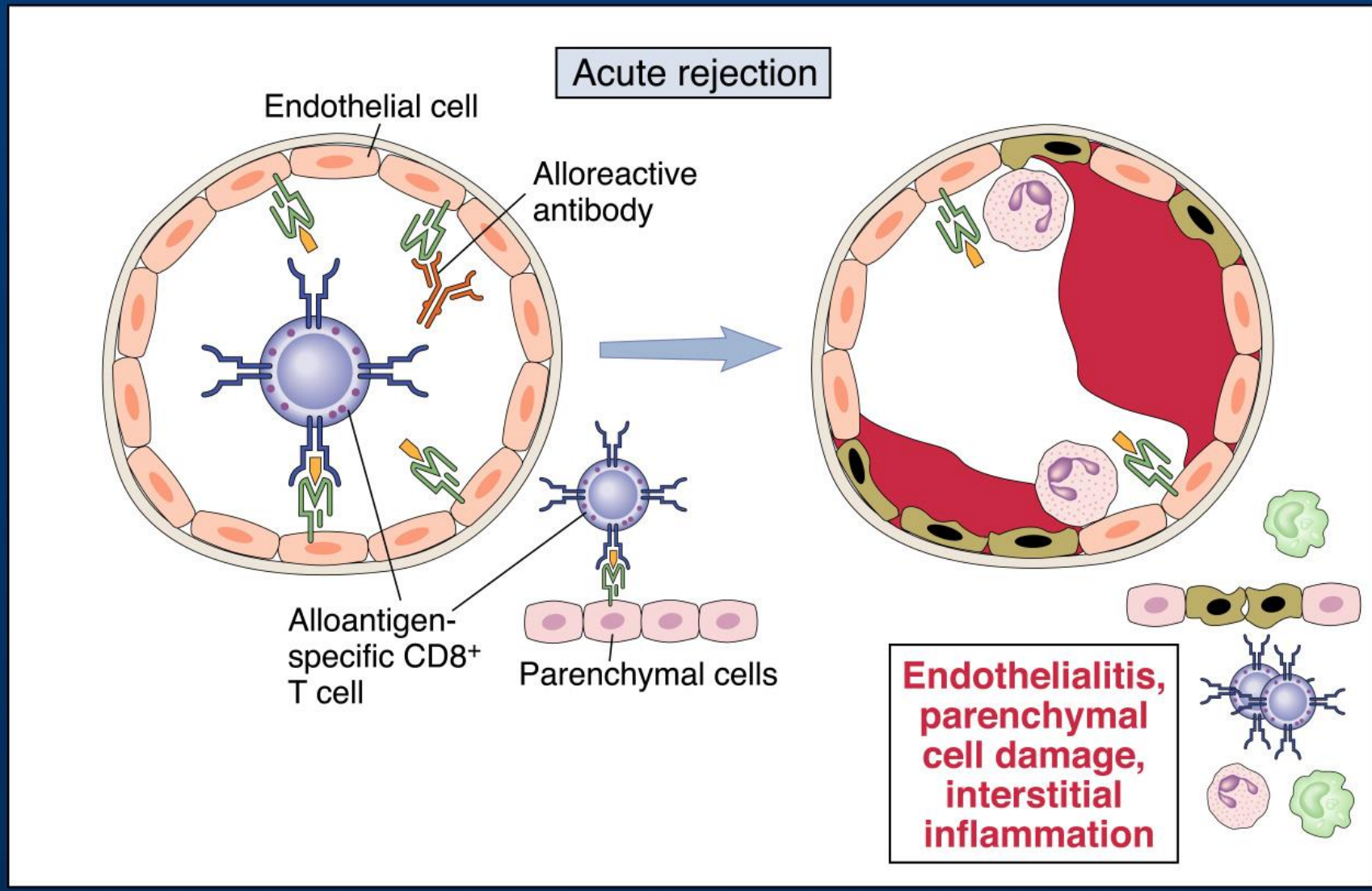
Effector mechanisms (purple blocks) involved in allograft rejection

Immune mechanisms of graft rejection (a)



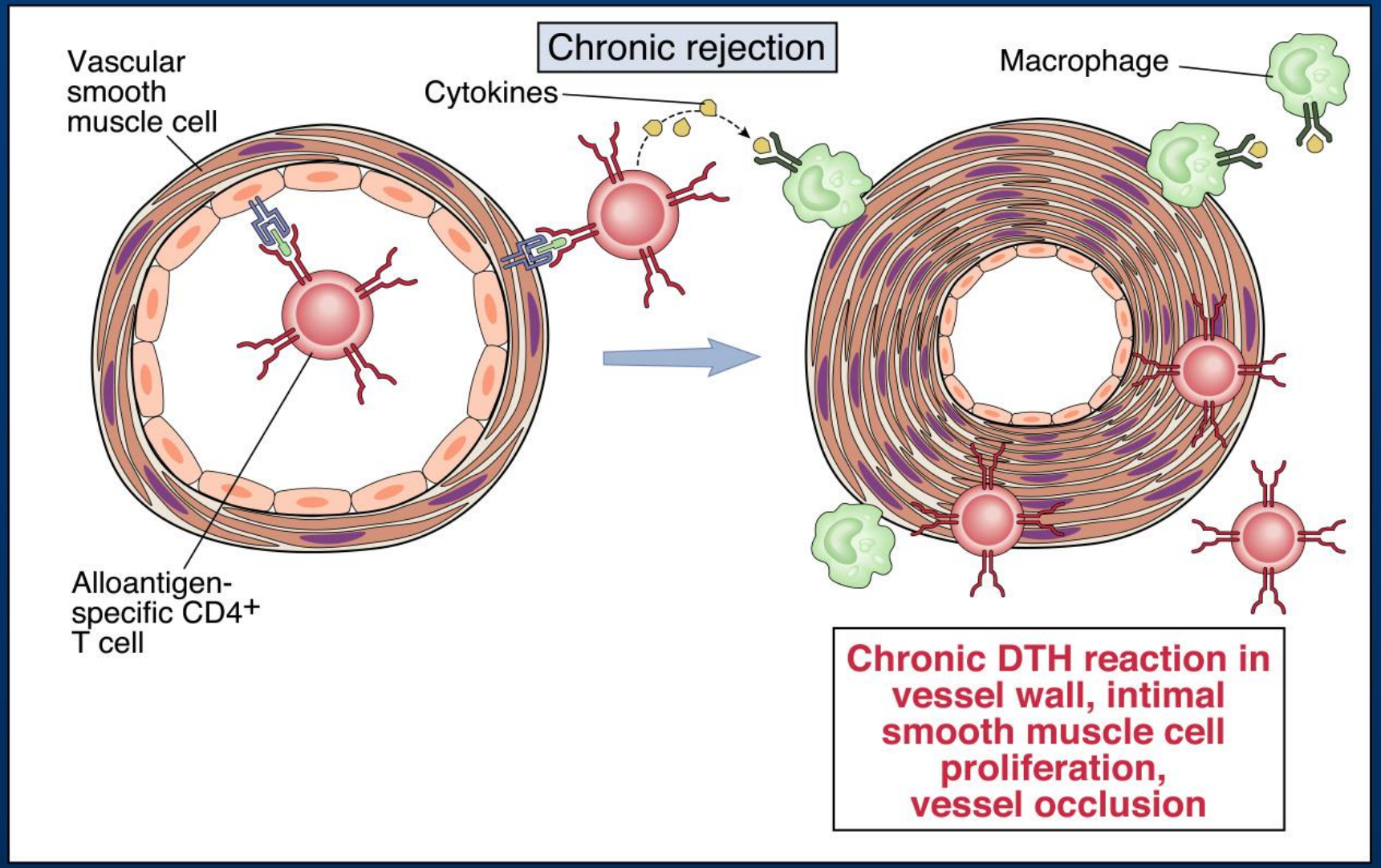
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-7a

Immune mechanisms of graft rejection (b)

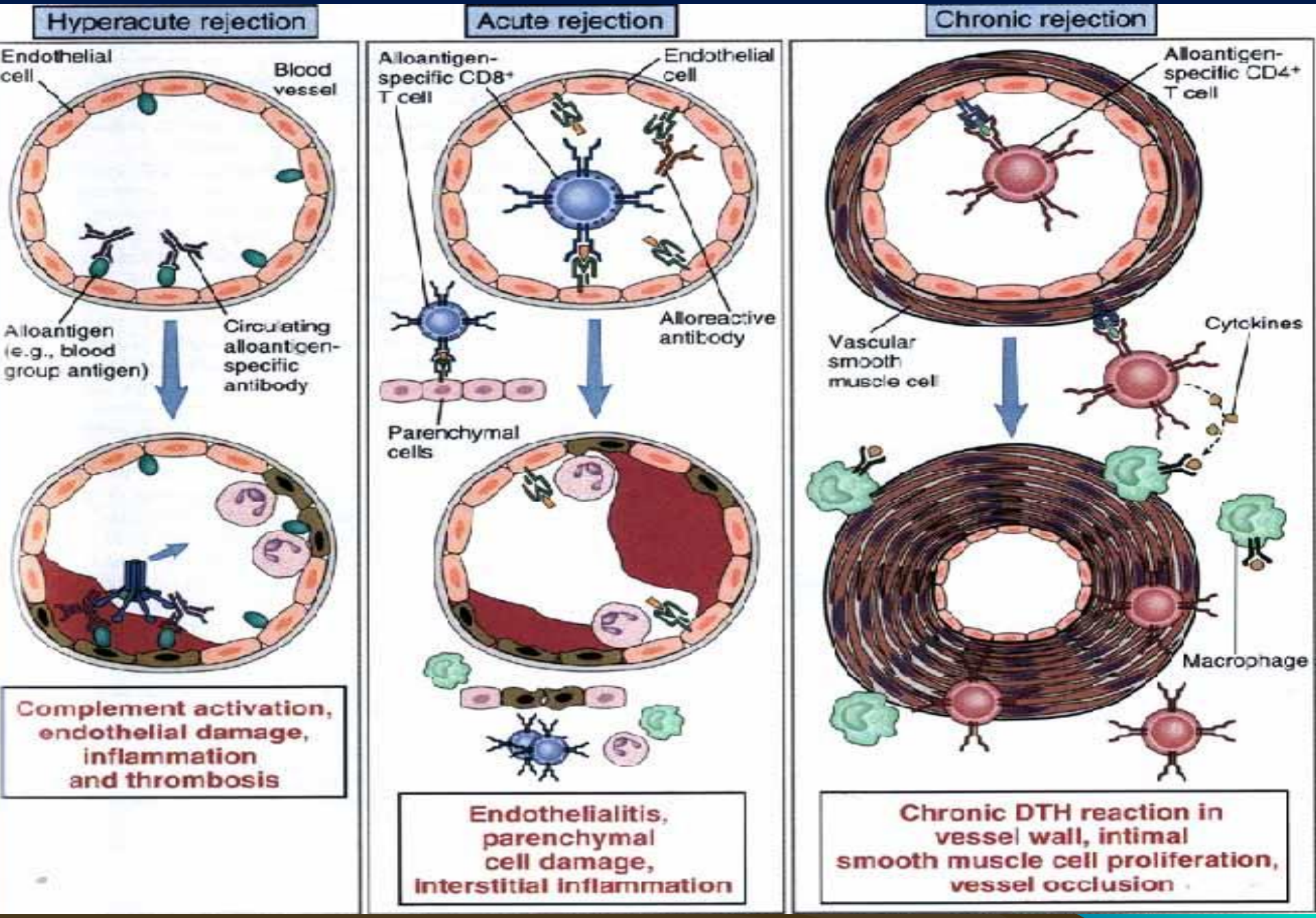


From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-7b

Immune mechanisms of graft rejection (c)



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-7c


Hyperacute rejection
Endothelial cell
Blood vessel
Alloantigen (e.g., blood group antigen)
Circulating alloantigen-specific antibody
Complement activation, endothelial damage, inflammation and thrombosis
Acute rejection
Alloantigen-specific CD8+ T cell
Endothelial cell
Alloreactive antibody
Parenchymal cells
Endothelialitis, parenchymal cell damage, interstitial inflammation
Chronic rejection
Alloantigen-specific CD4+ T cell
Vascular smooth muscle cell
Cytokines
Macrophage
Chronic DTH reaction in vessel wall, intimal smooth muscle cell proliferation, vessel occlusion

Zones of immunological privilege

- Certain sites of the human body have immune privilege, meaning they are able to tolerate the introduction of antigens without eliciting an inflammatory immune response. Grafts are normally recognised as foreign antigen by the body and attacked by the immune system.
- However in immune privileged sites, tissue grafts can survive for extended periods of time without rejection occurring .

- Transplants into zones of immunological privilege have proven highly successful.
- These sites may include the brain, the eyes, the placenta and the fetus, and the testicles (sometimes, also referring articular cartilage).
- For example, since there are few blood vessels in the cornea, there is a very low rate (about 20%) of corneal graft rejection.
- There has even been some success transplanting fetal pig neural tissue into the brains of Parkinson's disease patients.

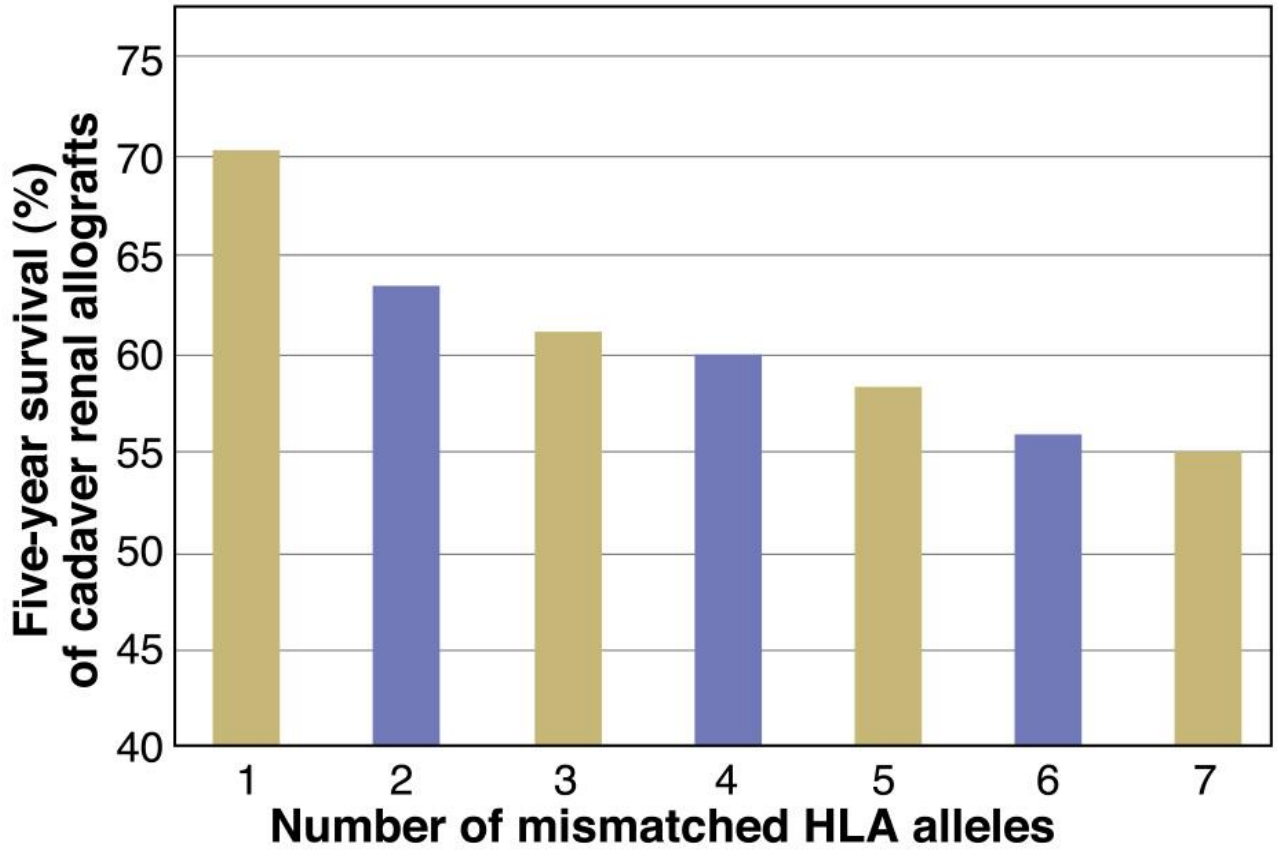
The converse of graft rejection is graft-versus-host disease (GVHD).

Transplantation of hematopoietic stem cells (HSCs) enriched from peripheral blood, bone marrow, or fetal cord blood is a successful therapy for some tumors derived from bone marrow precursor cells, such as certain leukemias and lymphomas. By replacing genetically defective stem cells with normal donor ones, HSC transplantation can also be used to cure some primary immunodeficiency diseases and other inherited diseases due to

defective blood cells, such as the severe forms of thalassemia.

In leukemia therapy, the recipient's bone marrow, the source of the leukemia, must first be destroyed by a combination of irradiation and aggressive cytotoxic chemotherapy. One of the major complications of allogeneic HSC transplantation is GVHD, in which mature donor T cells that contaminate preparations of HSCs recognize the tissues of the recipient as foreign, causing a severe inflammatory disease characterized by rashes, diarrhea, and liver disease.

Role of HLA matching in allograft survival



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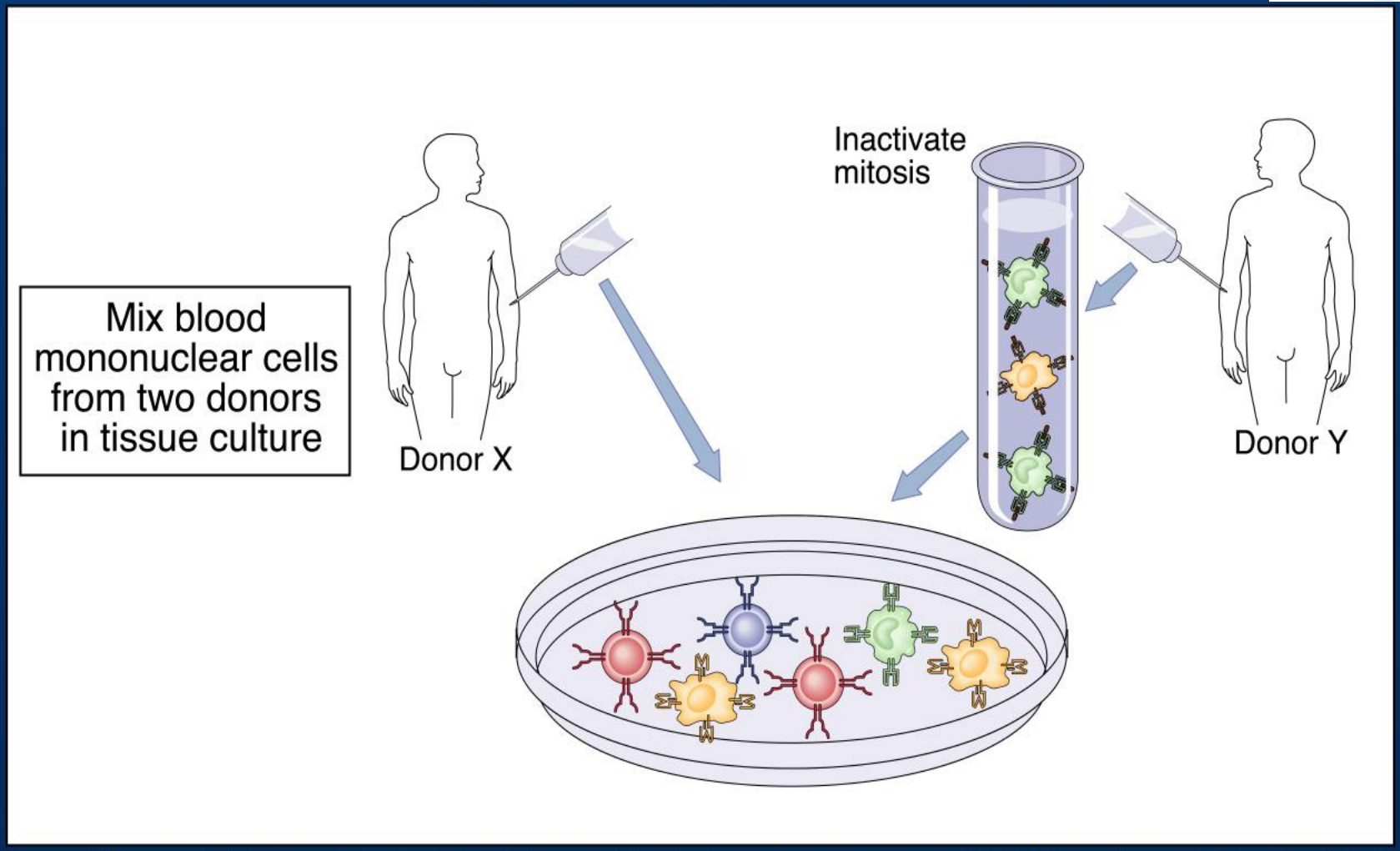
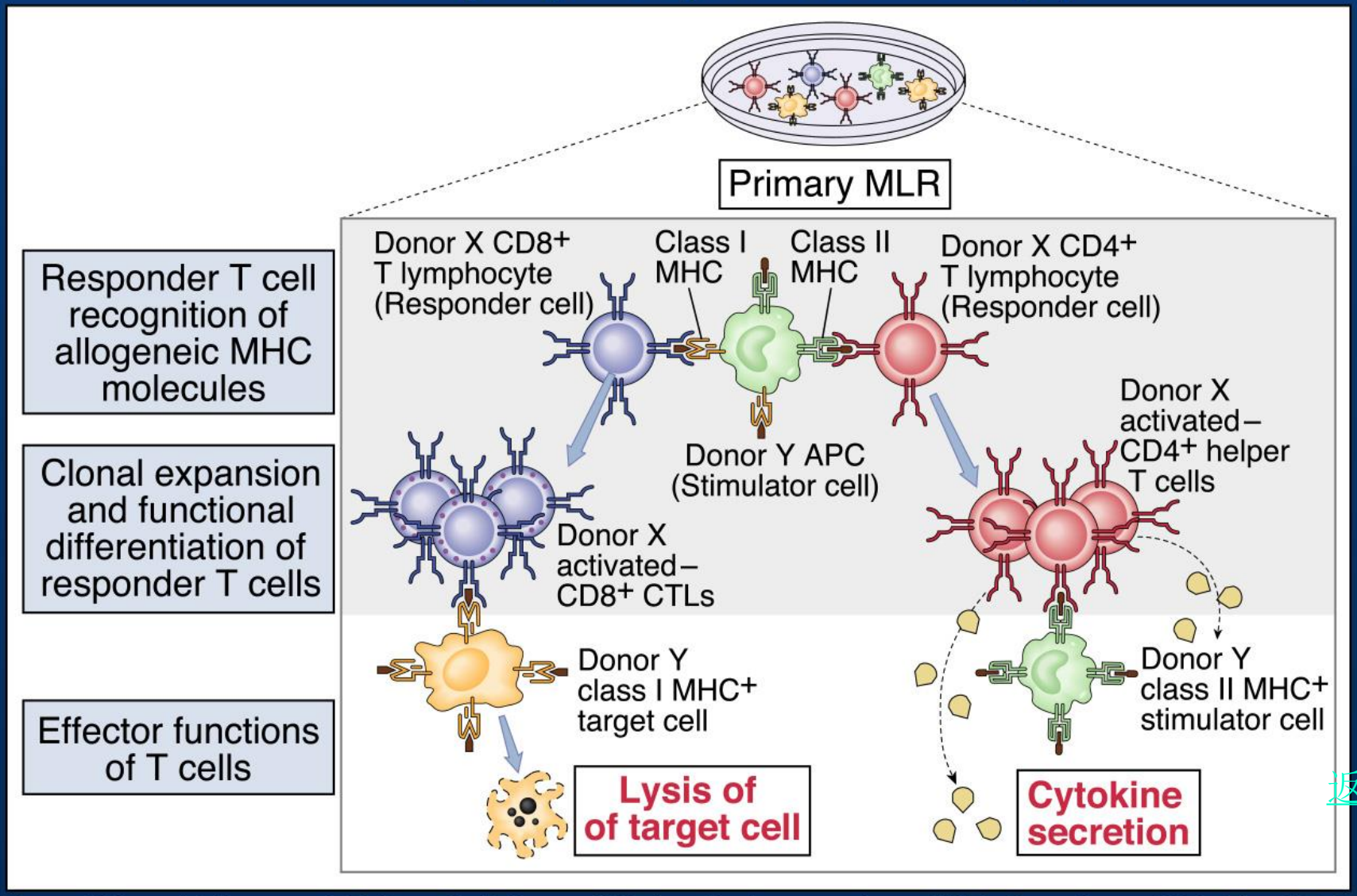
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-8b

Mixed lymphocyte reaction (a)



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-5a

Mixed lymphocyte reaction (b)



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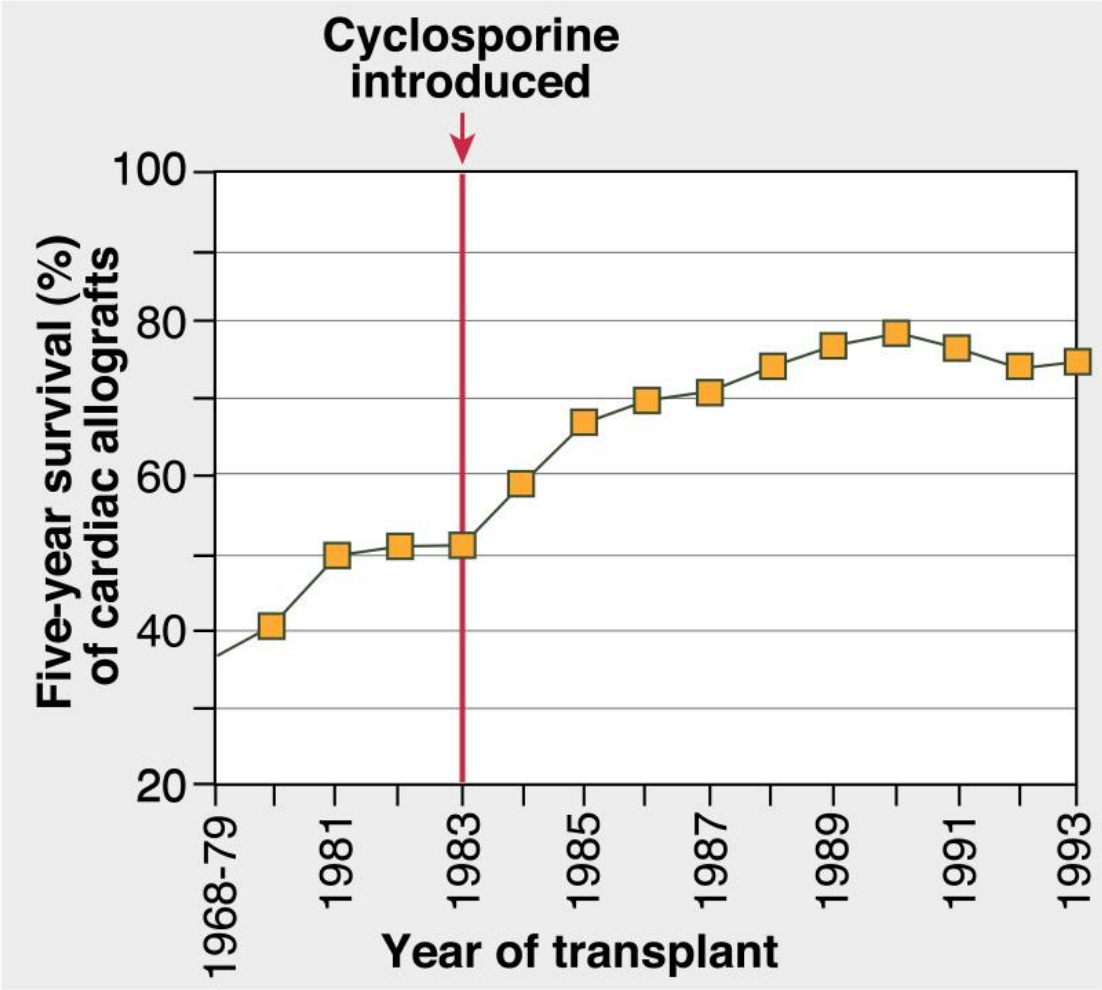
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-5b

Influence of cyclosporin A on graft survival



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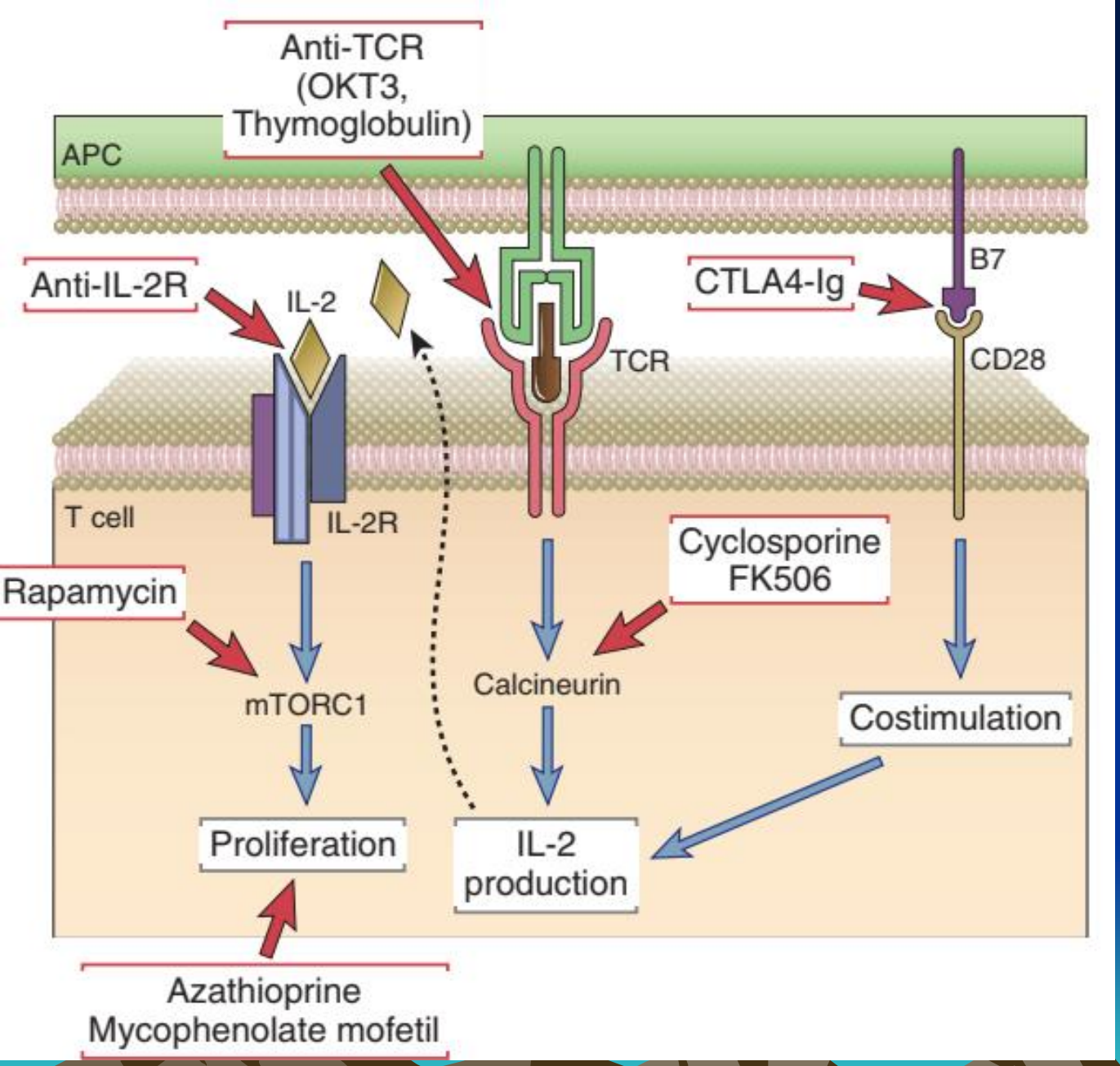
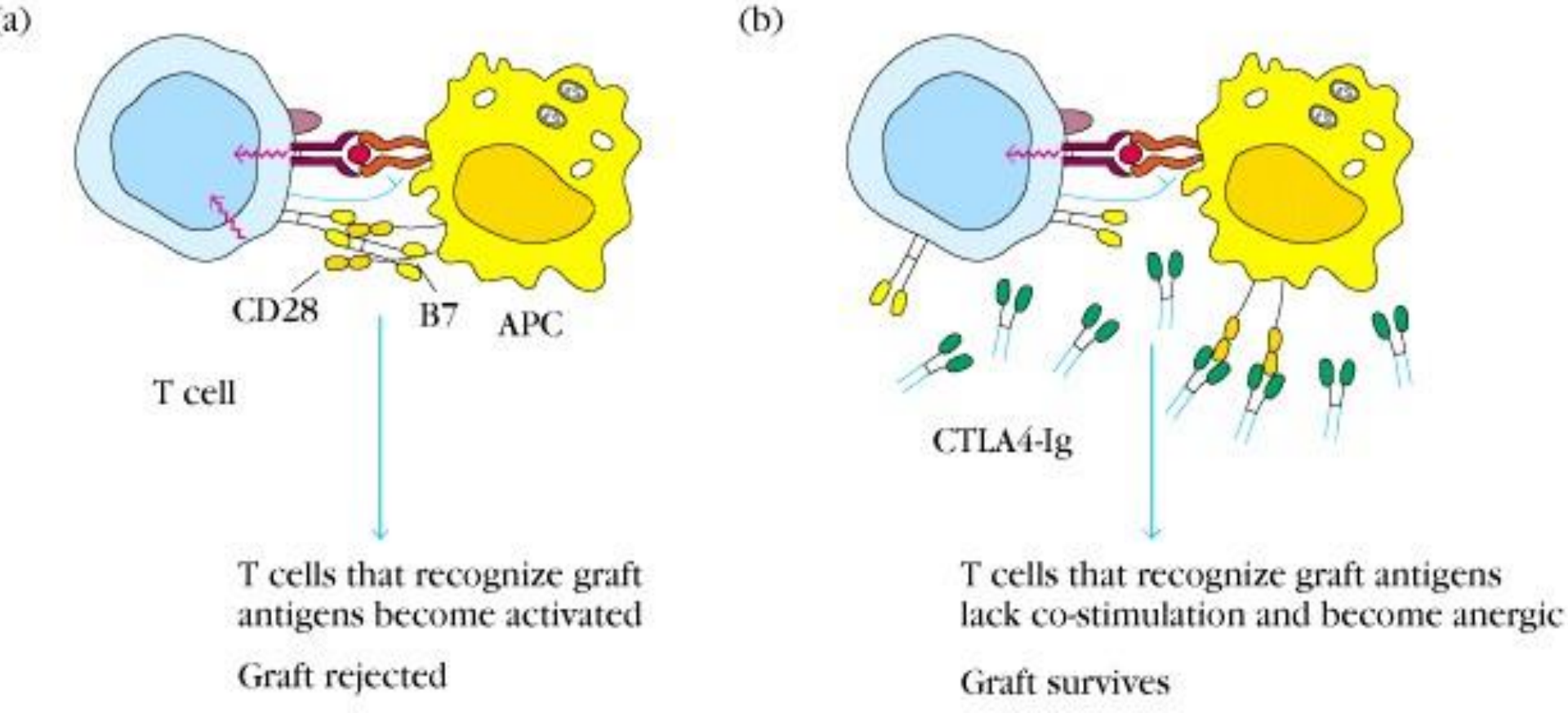
From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 16-08a



Each major category of drugs used to prevent or to treat allograft rejection is shown along with the molecular targets of the drugs.

Mechanisms of action of immunosuppressive drugs

- **Monoclonal antibodies can block T-cell activation and binding, extending the life of transplanted organs.**
- **Soluble fusion proteins can be made with block costimulatory signals necessary for T-cell activation.**

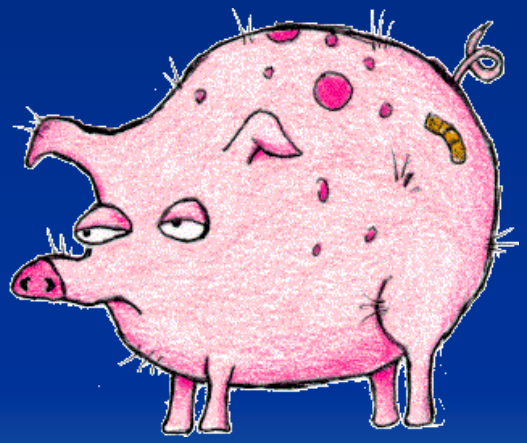


Which animals can be able to be used as source of transplant organs

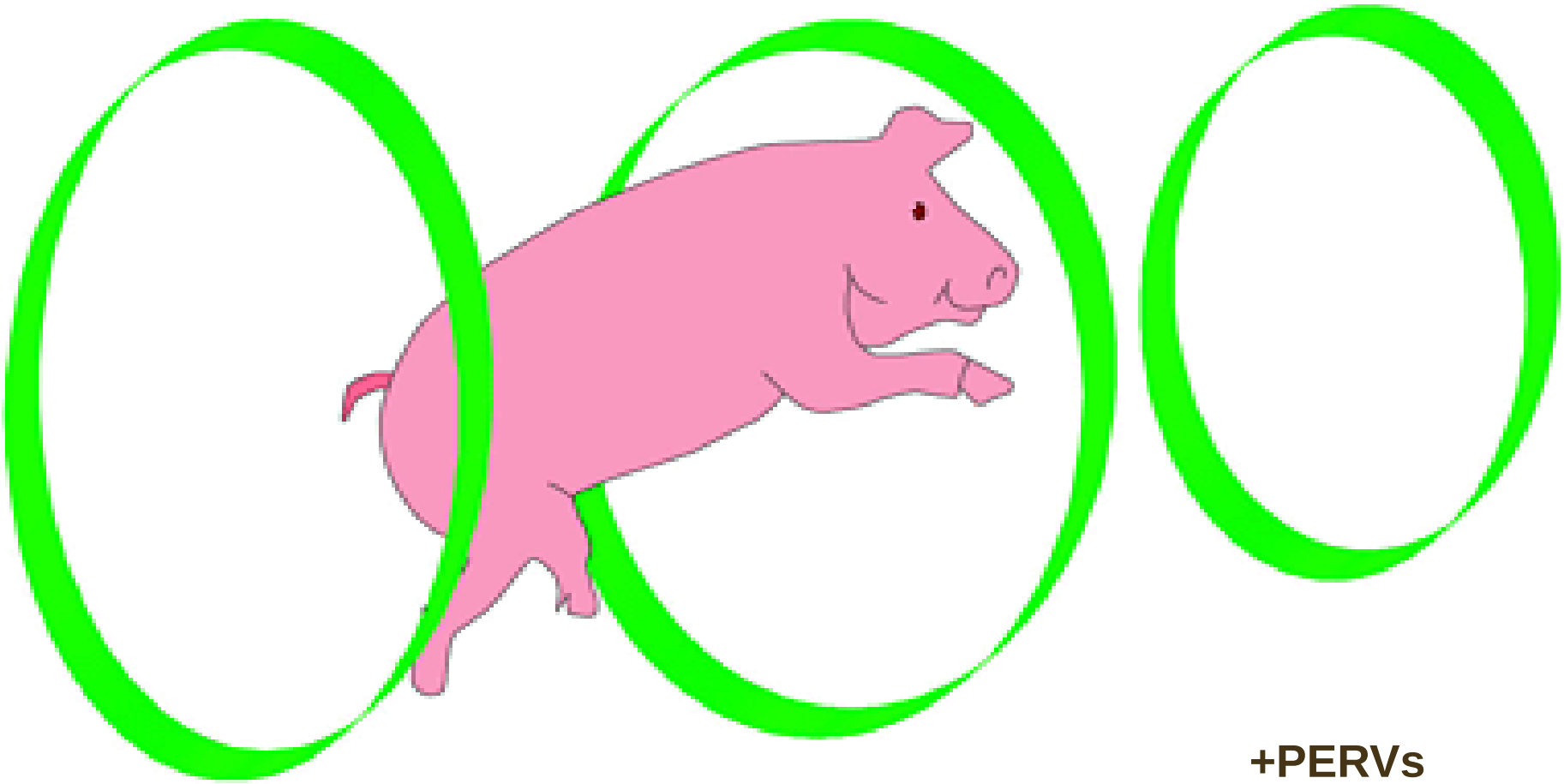
1. The Chimpanzee:
Its DNA sequence differs from humans by only 2%

2. The Baboon:
Its organs are too small for a large adult human

3. The Pig:
Surprisingly similar to humans' anatomy and physiology



Hoops for Xenotransplantation



Hyperacute rejection

Acute vascular rejection

+PERVs

Pig Endogenous Retroviruses

Cellular rejection

Current Opinion in Immunology

Tissue Engineering

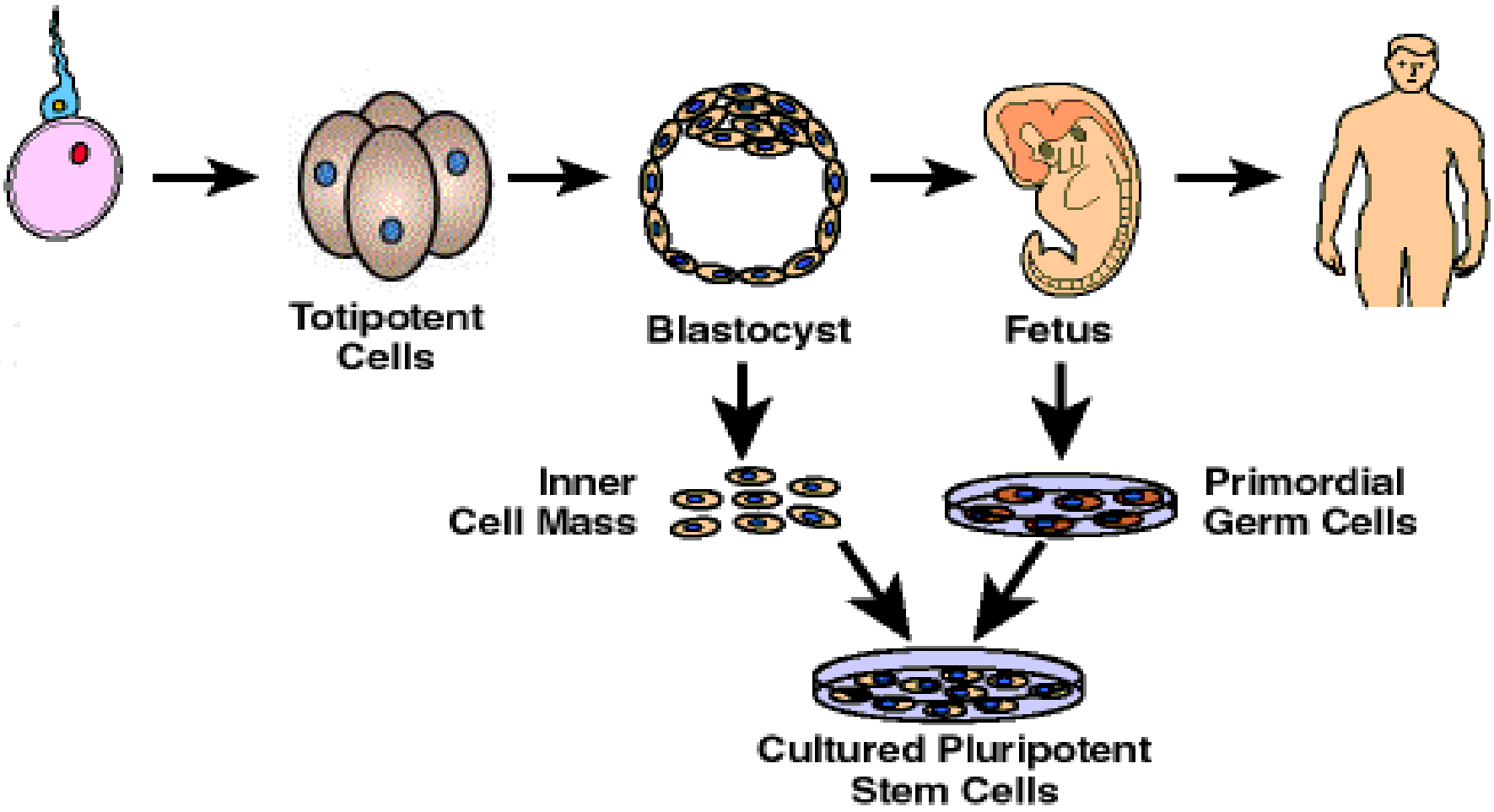
Digestive Tract

Vessel

Skin

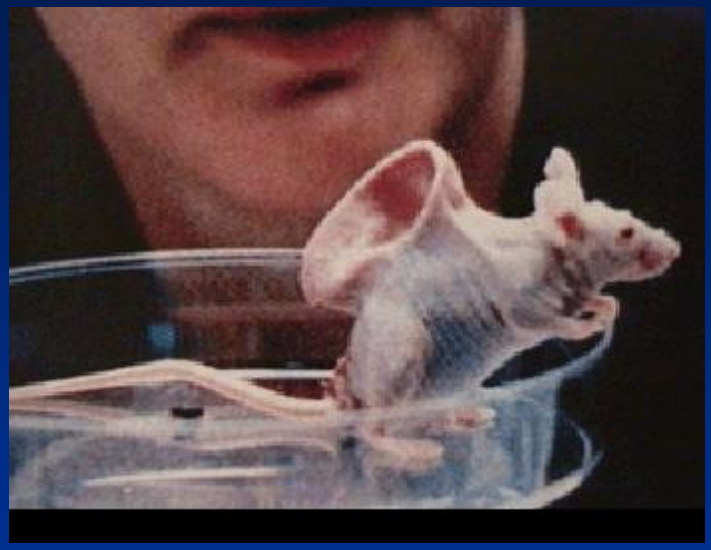
Nerve

Bone


Totipotent
Cells
Blastocyst
Fetus
Inner
Cell Mass
Primordial
Germ Cells
Cultured Pluripotent
Stem Cells

Organ breeding

- A transgenic animal carries a foreign gene inserted into its genome.



- The transgenic animal shows the specific characteristics which are coded on the inserted gene.

→ A gene which is responsible for the construction of a human organ makes the organism produce the organ additionally.

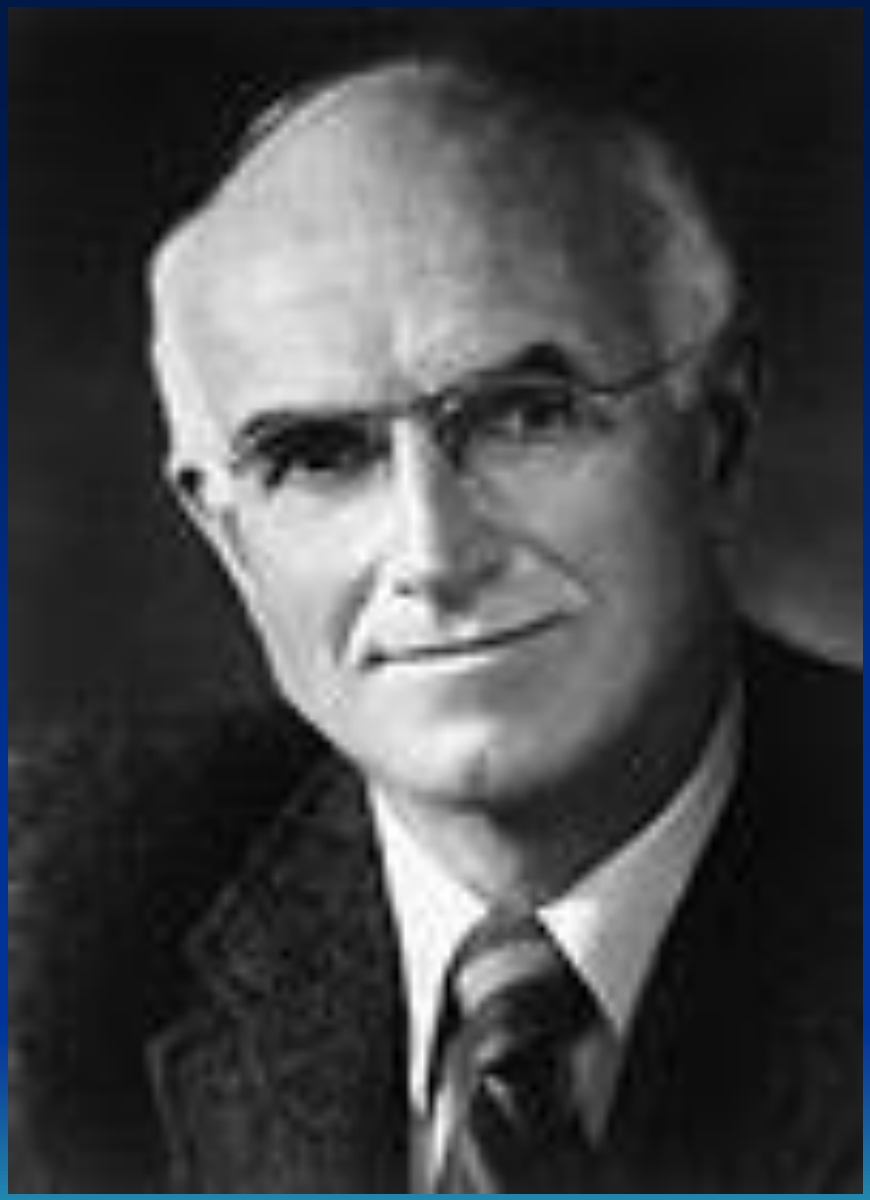
Summary

- Clinical transplantation is now an everyday reality, its success built on MHC matching, immunosuppressive drugs, and technical skill. However, even accurate MHC matching does not prevent graft rejection; other genetic differences between host and donor can result in allogeneic proteins whose peptides are presented as minor histocompatibility antigens by MHC molecules on the grafted tissue, and responses to these can lead to rejection.

- Because we lack the ability to specifically suppress the response to the graft without compromising host defense, most transplants require generalized immunosuppression of the recipient. This can be toxic and increases the risk of cancer and infection. The fetus is a natural allograft that must be accepted-it almost always is-or the species will not survive. Tolerance to the fetus might hold the key to inducing specific tolerance to grafted tissues, or it might be a special case not applicable to organ replacement therapy.

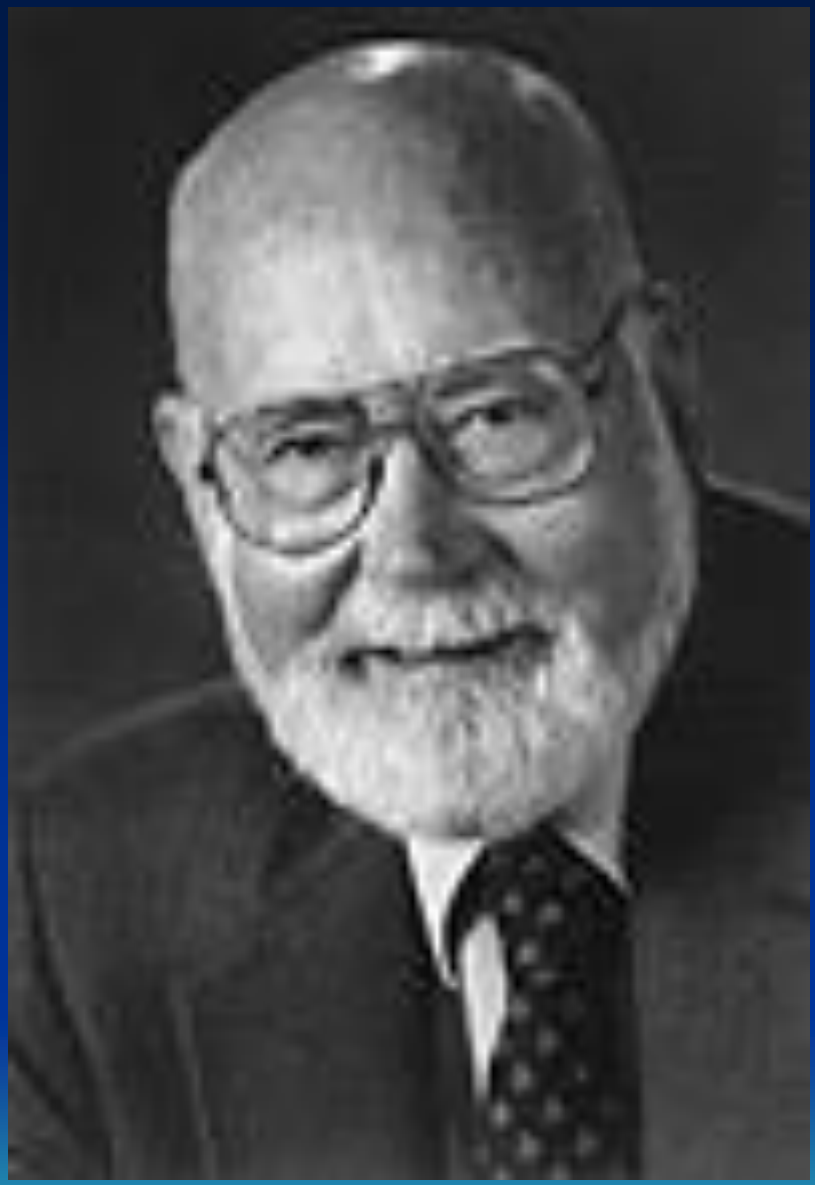
Transplantation: A Time-line

- 1902 Albert, auto-transplantation of a dog kidney.
- 1905 Carrel, allografts failed after brief function.
- 1909 Unger, xenograft (monkey to human).
- 1914 Carrel, research into rejection was required.
- 1943 Gibson and Medawar, skin transplants.
- 1954 Murray and Hume, human renal transplants.
- 1960 Calne/Kuss, 6-mercaptopurine.
- 1962 Hamberger/Terasaki, tissue typing.
- 1970's HLA typing introduced.
- 1973 Opelz, Transfusion effect described.
- 1978 CyA discovered. HLA-DR typing introduced.
- 1981 Cosimi, OKT3 introduced for acute rejection.
- 1989 Starzl, FK506 introduced.
- 1993 Mycophenolate mofetil introduced.
- 2017? Xenografts? Donor Specific Tolerance



JOSEPH E. MURRAY（1919～）

The first case of **renal transplantation** (1990NP)



E. DONNALL THOMAS（1920～）

The first case of **bone marrow transplantation** (1990NP)

Concepts:

1. Allograft
2. Xenograft
3. HVGR and GVHD
4. Mixed Lymphocytic Rejection
5. Acute Reaction and Chronic Rejection

Questions:

1. Classify grafts. Please explain the graft-versus-host reaction!
2. Discuss potential mechanisms for and differences between hyperacute, acute, and chronic rejection.