Outline

Solid organ transplantation
- Concepts
- Hyperacute rejection
- Acute rejection
- Chronic rejection

Bone marrow transplantation
- Graft-versus-host
- Graft-versus-tumor

Pregnancy
- Rh factor

History of Organ Transplantation

1905: First successful cornea transplant by Eduard Zirm (Czech Republic)

1954: First successful kidney transplant by Joseph Murray (USA)

1966: First successful pancreas transplant by Richard Lillehei and William Kelly (USA)

1967: First successful liver transplant by Thomas Starzl (USA)

1967: First successful heart transplant by Christiaan Barnard (South Africa)

1968: First successful human bone marrow transplant by Robert Good (USA)

1981: First successful heart/lung transplant by Bruce Reitz (USA)

1983: First successful lung lobe transplant by Joel Cooper (Canada)

1986: First successful double-lung transplant by Joel Cooper (Canada)

1995: First successful laparoscopic live-donor nephrectomy by Lloyd Ratner and Louis Kavoussi (USA)

1998: First successful live-donor partial pancreas transplant by David Sutherland (USA)

1998: First successful hand transplant (France)

1999: First successful tissue engineered bladder transplanted by Anthony Atala (USA)

2005: First successful partial face transplant (France)

2006: First jaw transplant to combine donor jaw with bone marrow from the patient, by Eric M. Genden (USA)

2008: First successful complete full double arm transplant by Edgar Biemer & colleagues (Germany)

2008: First baby born from transplanted ovary.

2008: First transplant of a human windpipe using a patient's own stem cells, by Paolo Macchiarini (Spain)

2010: First successful full face transplant, by Joan Pere Barret & colleagues (Spain)

Full Face Transplant

Norris, from left, in a high school photo, one taken before the transplant, a photo taken six days after the transplant and one from 114 days after the transplant. The final photo shows Norris in June 2013.

http://www.nydailynews.com/life-style/health/man-full-face-transplant-photographed-gq-article-1.1884074

Life After Face Transplant: Q&A With Patient Richard Lee Norris

Solid Organ Transplantation

- To replace damaged organs
  - Trauma
  - Auto immune

- Challenge
  - Limited source of donor
  - Long-term graft rejection

Graft Types

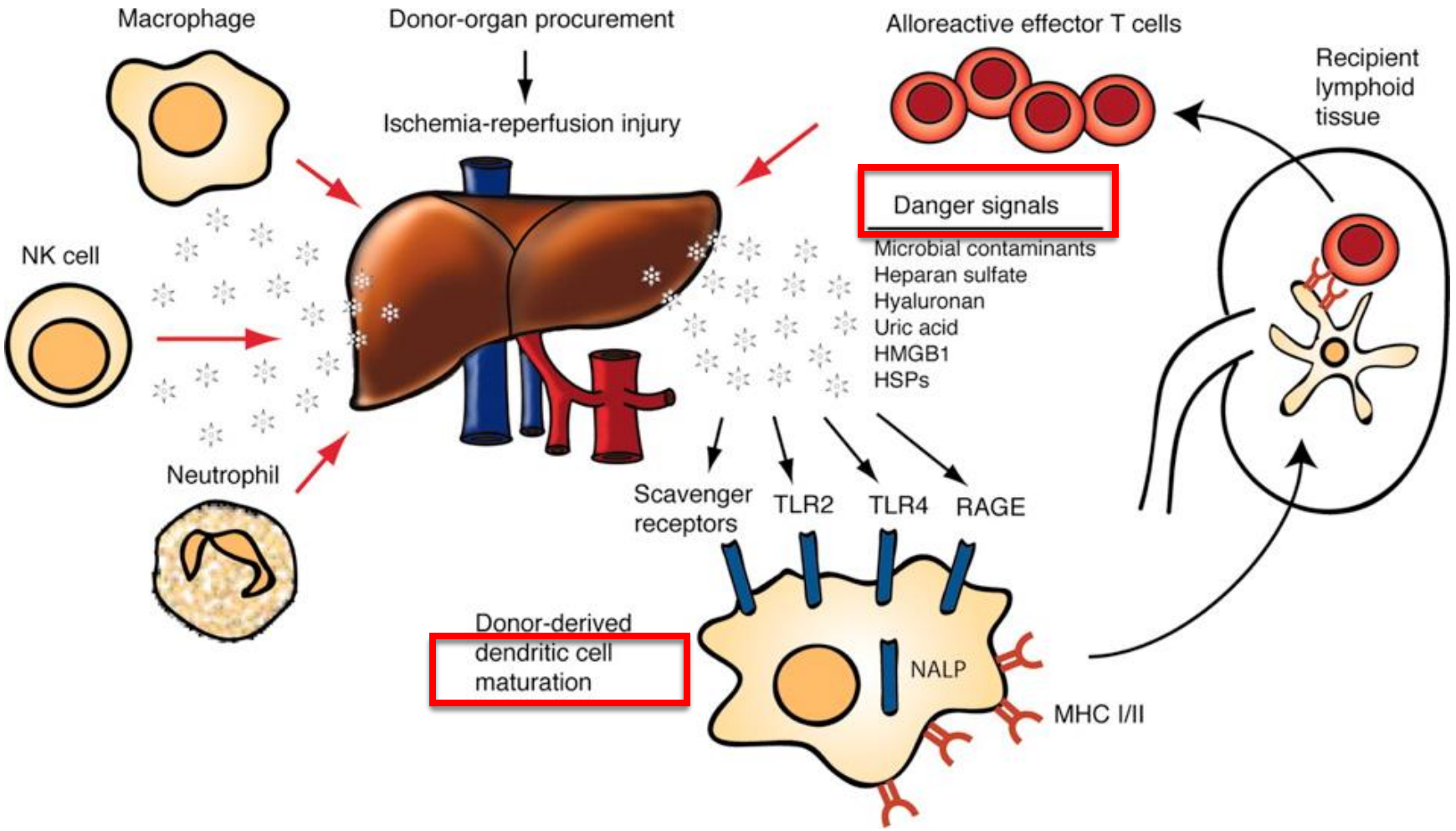
Autograft
- self graft (transplantation of ones own tissue)
- 100% success

Syngeneic graft
- genetically identical graft (identical donor tissue)
- 100% success

Allograft (allogeneic graft)
- unrelated graft (non-identical donor tissue, same specie) **Remember what happened to Medwar's mice**
- rejection 10-13 days post transplantation

Xenograft (from other species)

The Transplantation Procedure is Inflammatory



The Journal of Immunology, 2007, 178: 3558-3565.

Kidney Rejection

Normal kidney

Rejected kidney

Figure 15.6 The Immune System, 3ed. (© Garland Science 2009)

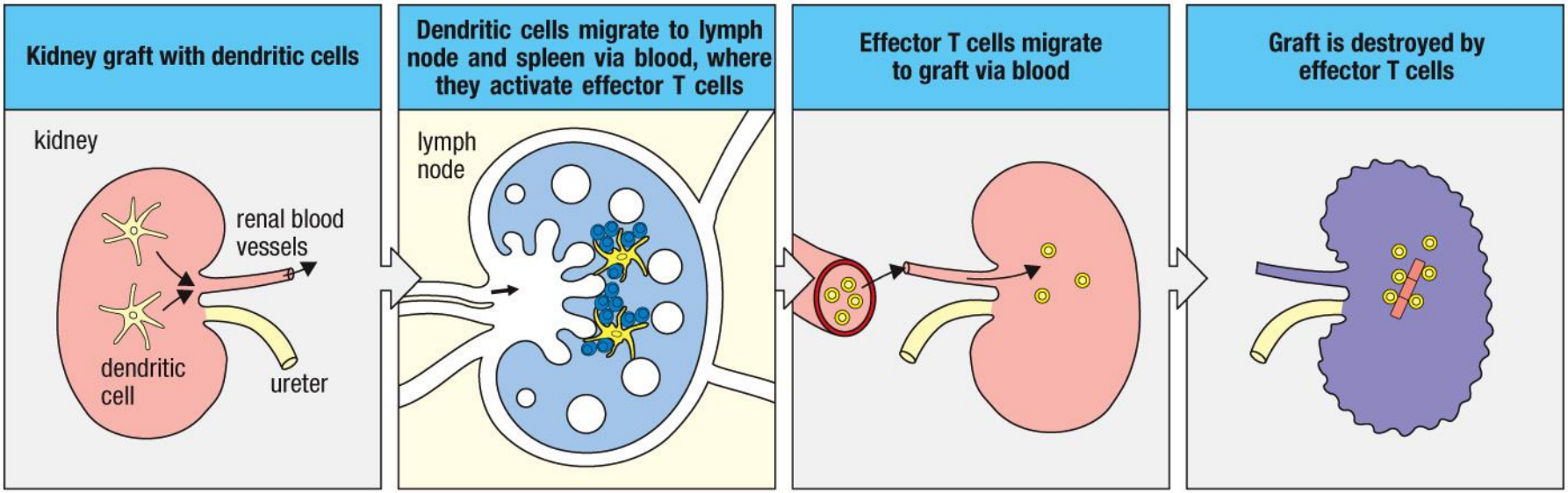


Figure 15.48 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Major Histocompatibility Complex

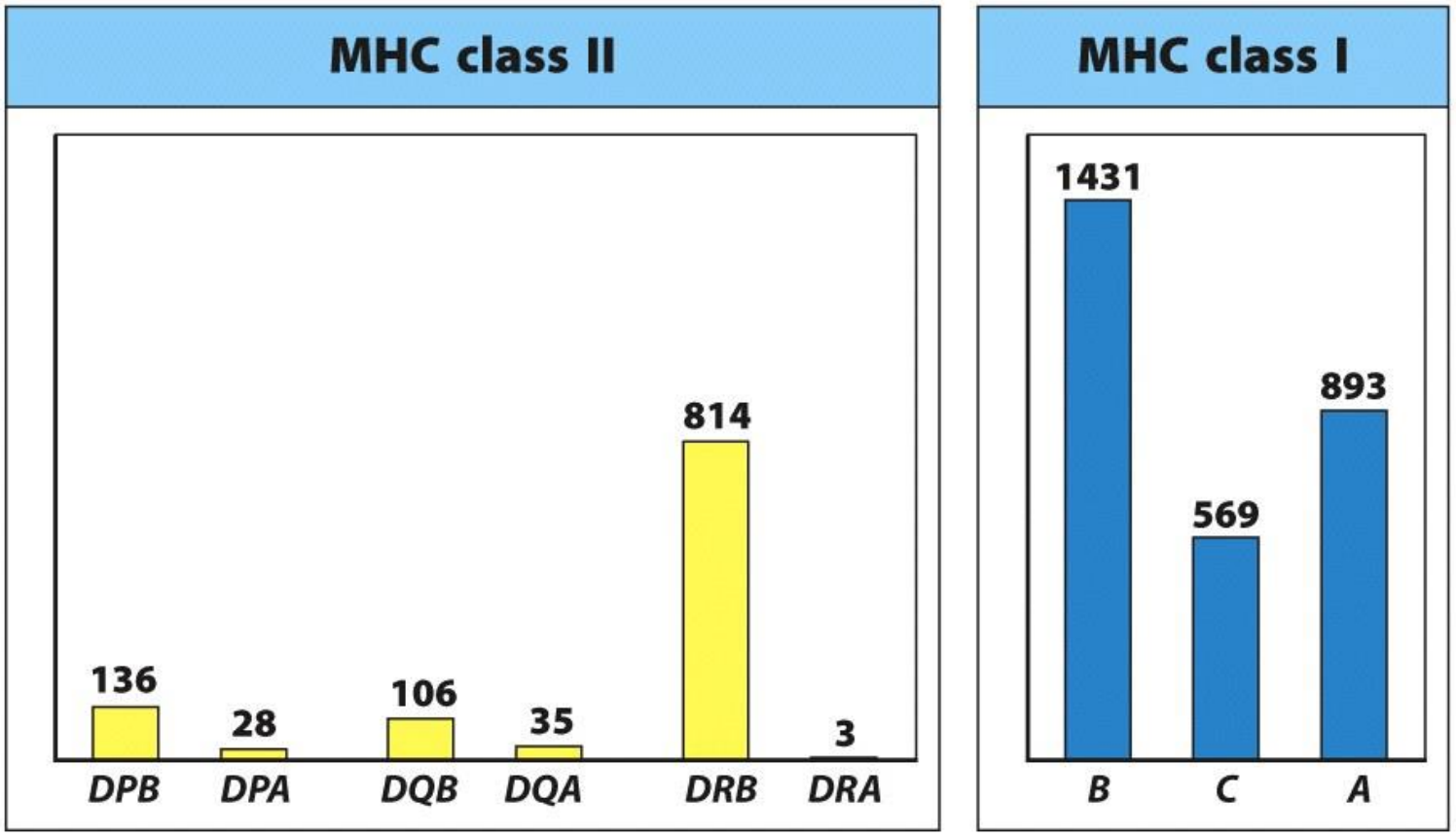


Figure 6.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Chance of perfect match: 1431x569x893x136x28x106x35x814x3= 2.5E19
Current world population: 7 billion=7E9

Complete MHC Matching May Not Be Enough to Ensure Graft Survival

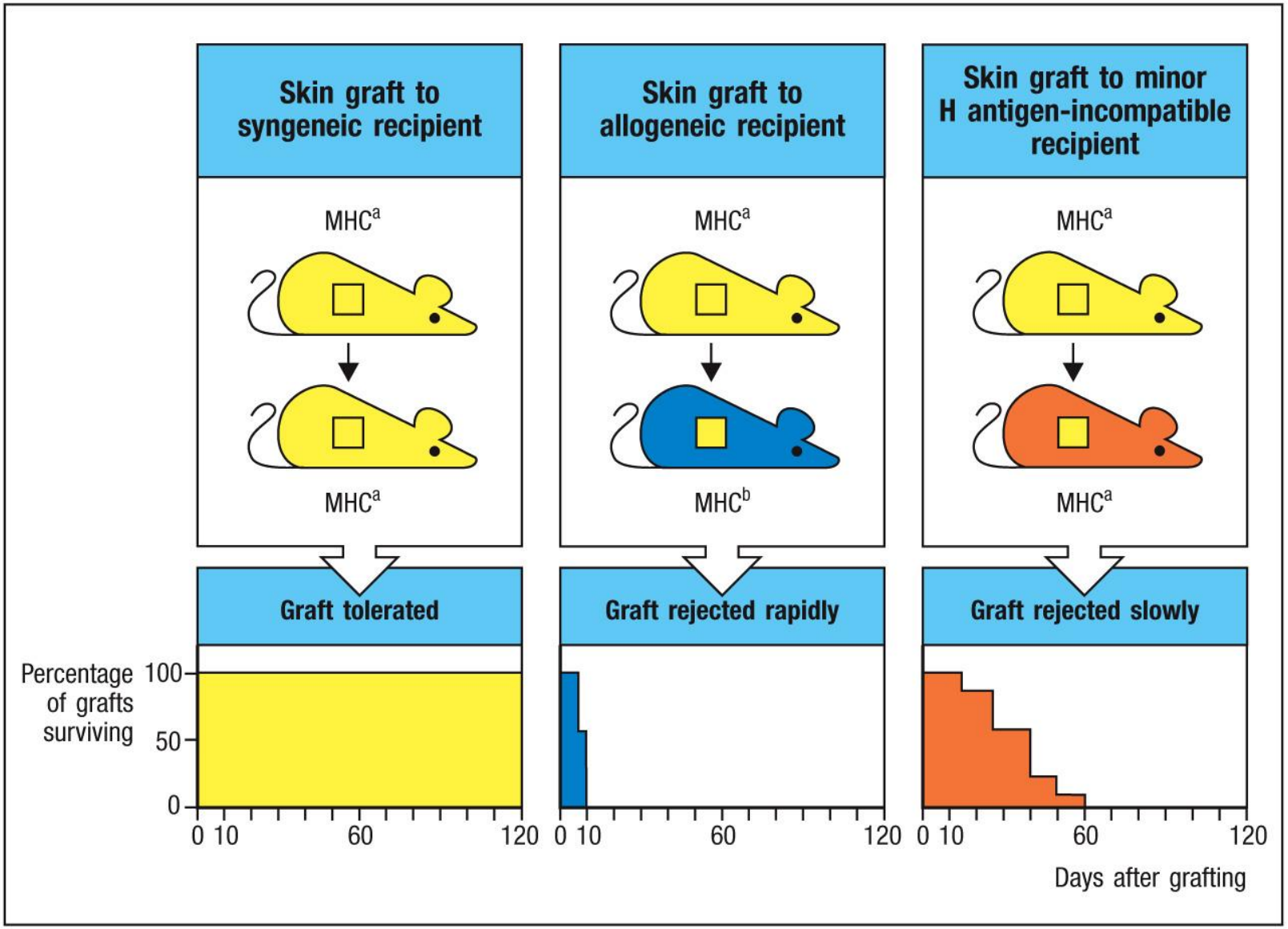
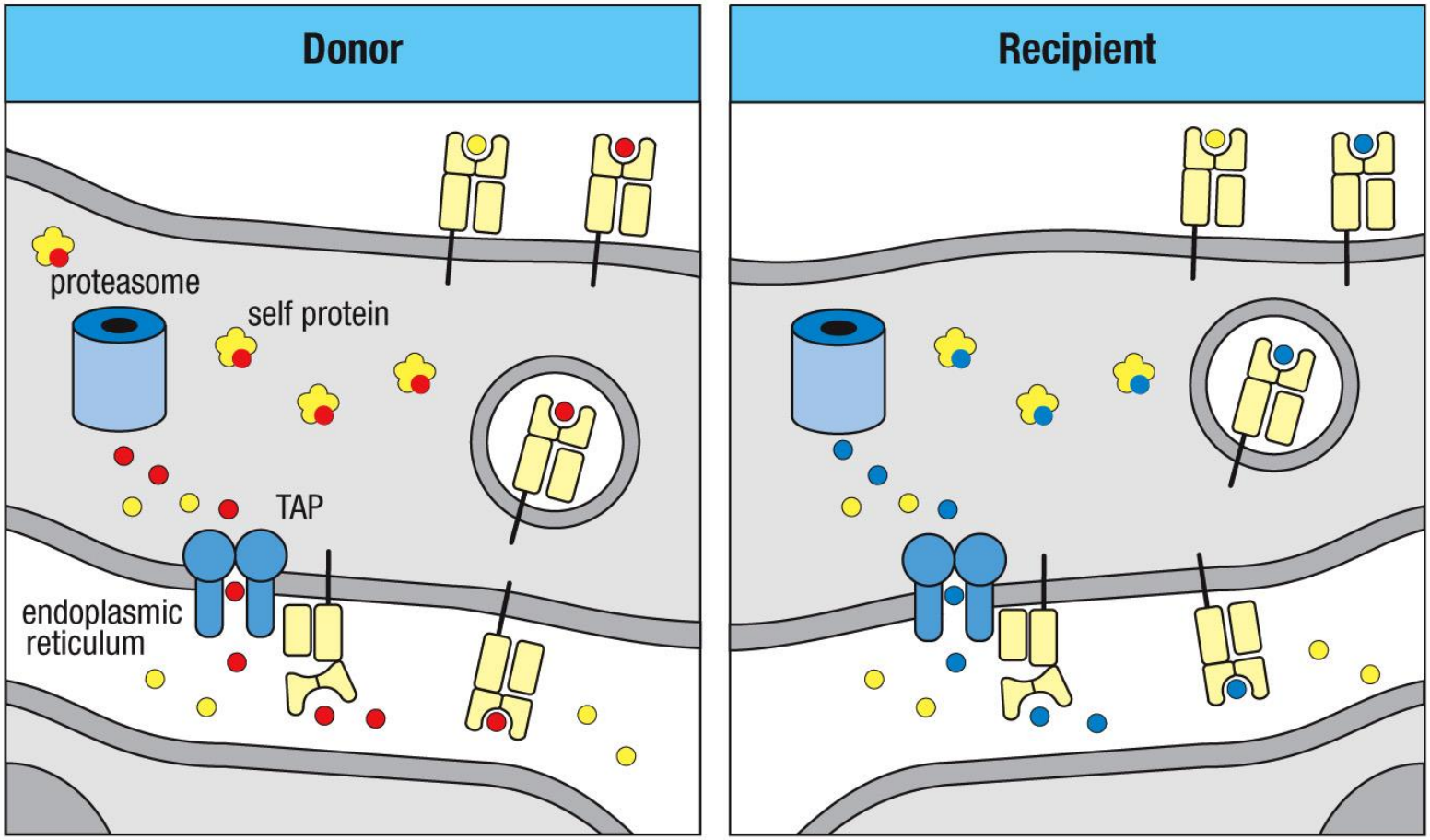


Figure 15.46 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Minor Histocompatibility

viral infected cells



Polymorphic self proteins that differ in amino acid sequence between individuals give rise to minor H antigen differences between donor and recipient

Figure 15.47 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Rejection is Accelerated in the Second Transplant

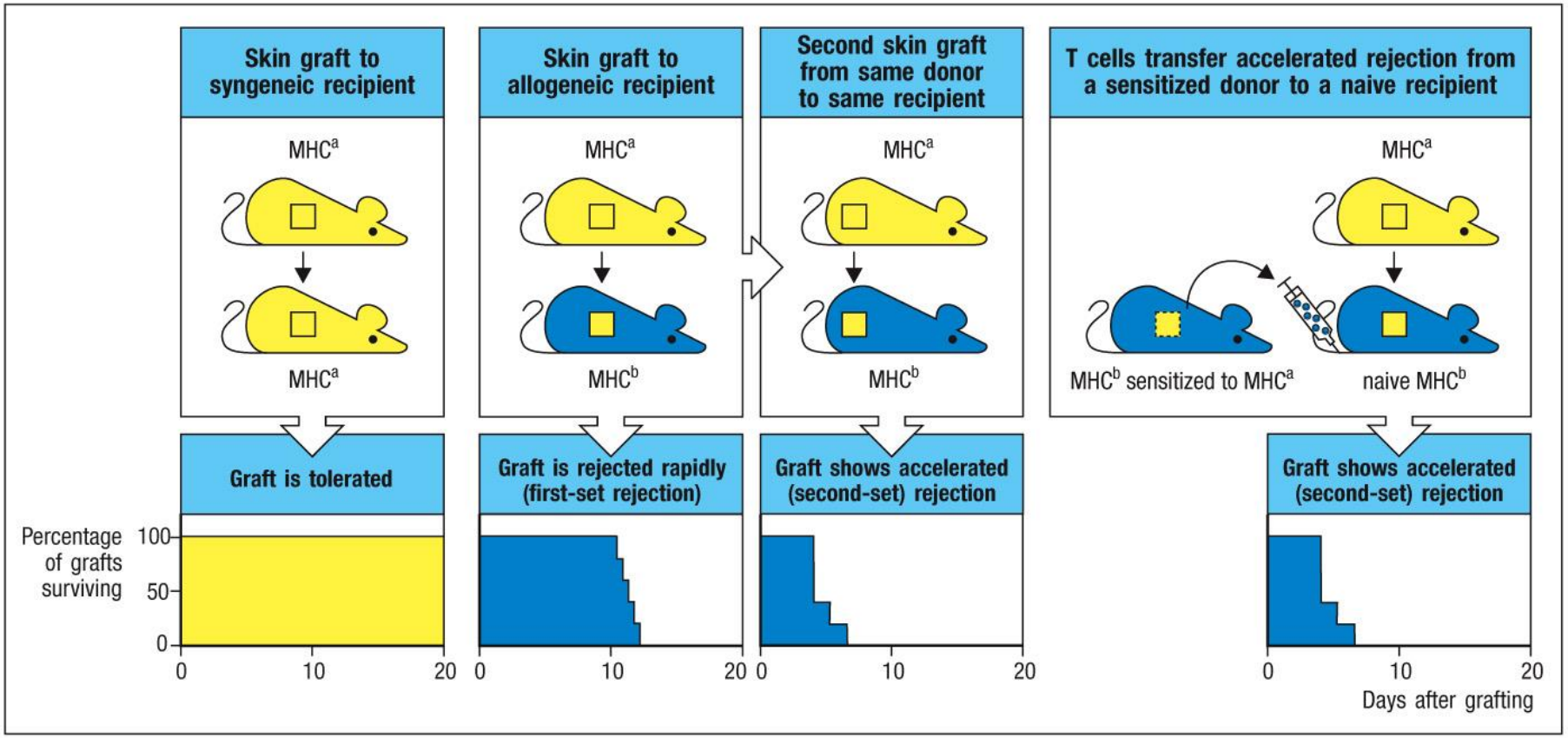


Figure 15.45 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immune Suppression

- Required and routinely applied in transplantation
- Required for life-time
- Except for self and identical twins

Immunosuppressive Drugs

Conventional immunosuppressive drugs in clinical use	
Immunosuppressive drug	**Mechanism of action**
Corticosteroids	Inhibit inflammation; inhibit many targets including cytokine production by macrophages
Azathioprine, cyclophosphamide, mycophenolate	Inhibit proliferation of lymphocytes by interfering with DNA synthesis
Cyclosporin A, tacrolimus (FK506)	Inhibit the calcineurin-dependent activation of NFAT; block IL-2 production and proliferation by T cells
Rapamycin (sirolimus)	Inhibits proliferation of effector T cells by blocking Rictor-dependent mTOR activation
Fingolimod (FTY270)	Blocks lymphocyte trafficking out of lymphoid tissues by interfering with signaling by the sphingosine-1-phosphate receptor

broad, adverse side effects

toxic

activation

retention

Figure 16.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Problem: Affect all Immune responses indiscriminately
Susceptible to infections and cancers

Immunosuppressive Drugs

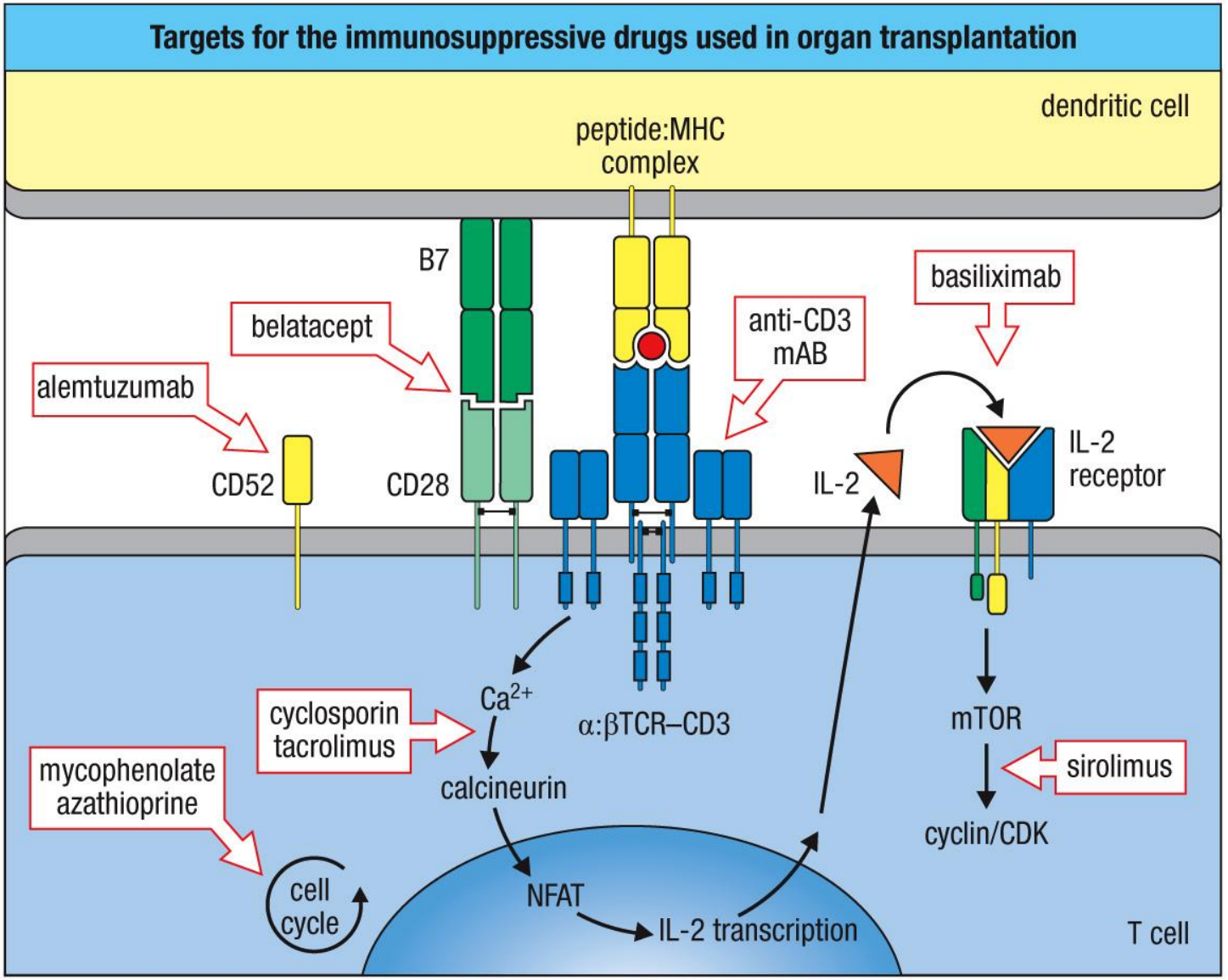


Figure 15.52 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Outline

Solid organ transplantation
- Concepts
- Hyperacute rejection
- Acute rejection
- Chronic rejection

Bone marrow transplantation
- Graft-versus-host
- Graft-versus-tumor

Pregnancy
- Rh factor

Hyperacute Rejection Is Mediated by Antibodies and Is Complement-Dependent

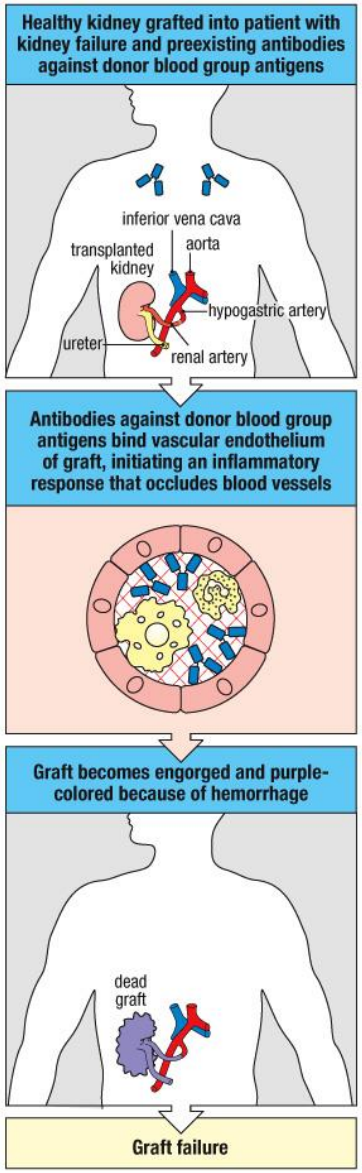
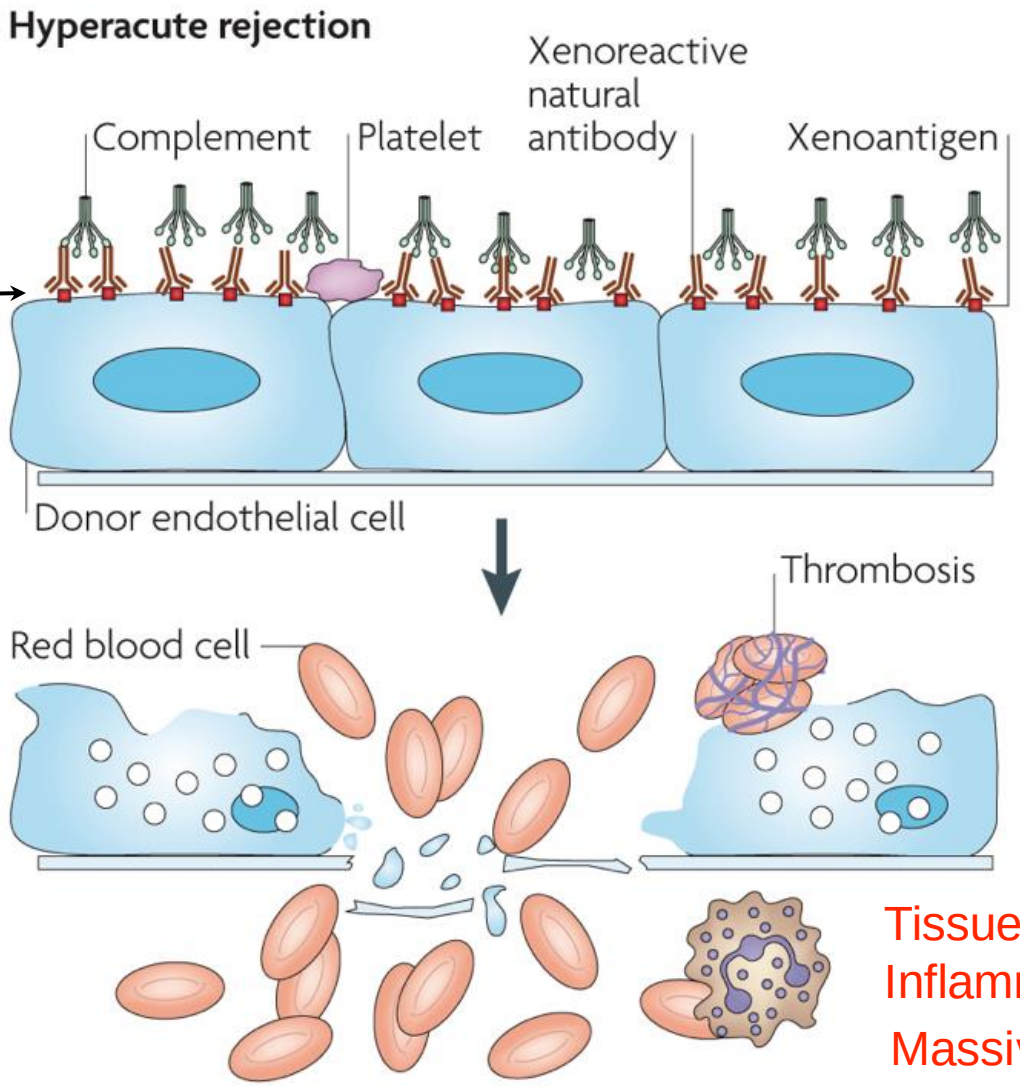


Figure 15.50 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Hyperacute Humoral Rejection

Timeframe: minutes-hours



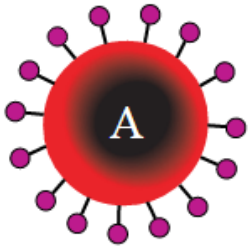
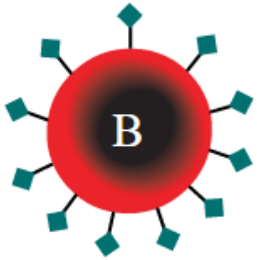
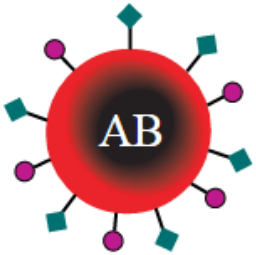
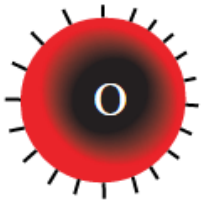
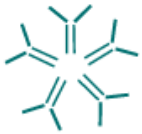
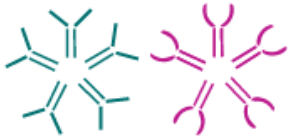
High level of alloantigens

Tissue destruction
Inflammation
Massive haemorrhage

Nature Reviews Immunology. v.7, p.519 (2007)

ABO antigens

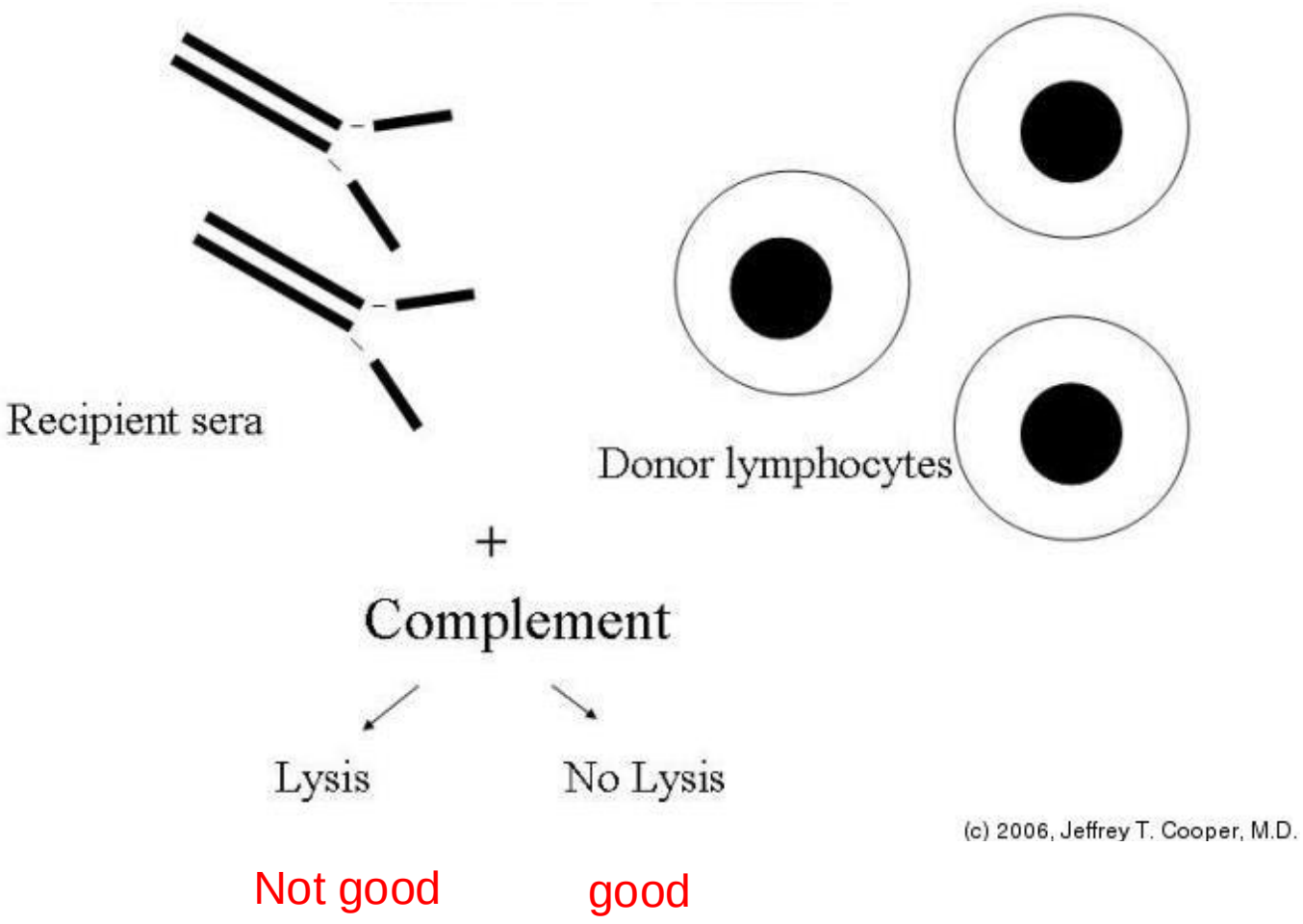
IgM antibodies produced during the first years of life
Antigens present on blood vessel as well

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma	 Anti-B	 Anti-A	None	 Anti-A and Anti-B
Antigens in Red Blood Cell	 A antigen	 B antigen	 A and B antigens	None

http://upload.wikimedia.org/wikipedia/commons/3/32/ABO_blood_type.svg

Cross Matching

Check for existing donor specific antibodies



Not good

good

Outline

Solid organ transplantation

- Concepts
- Hyperacute rejection-preexisting antibodies, min-hours
- Acute rejection- requires activation
- Chronic rejection

Bone marrow transplantation

- Graft-versus-host
- Graft-versus-tumor

Pregnancy

- Rh factor

Donor APCs Can Initiate Graft Rejection

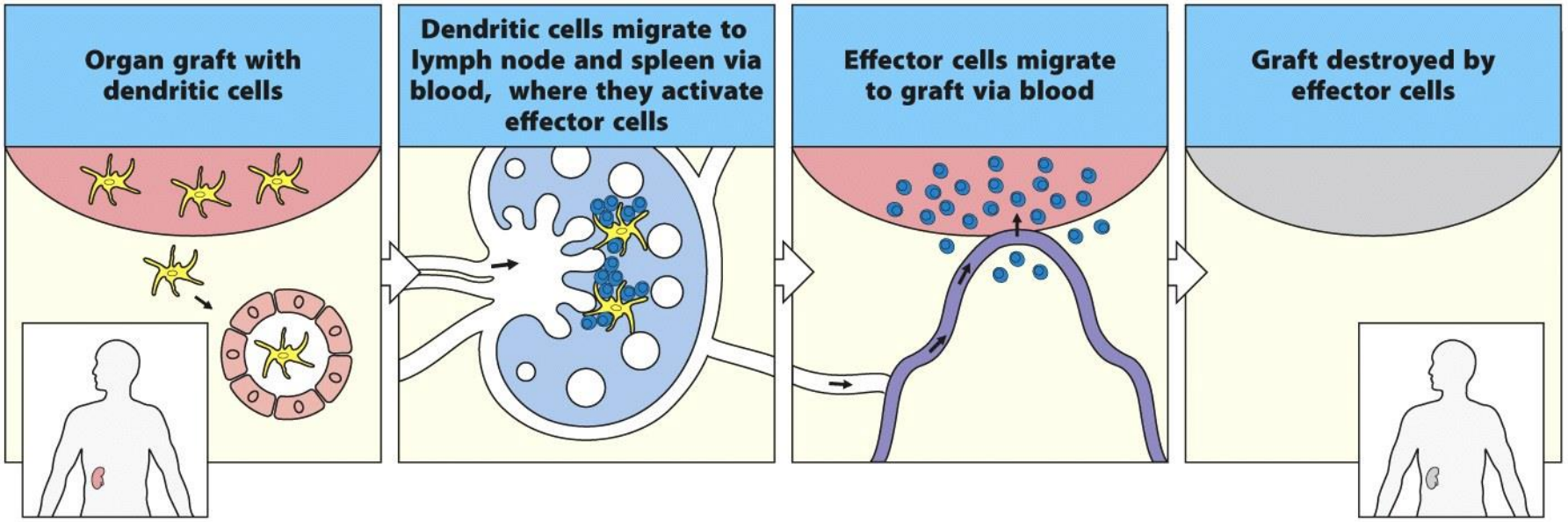


Figure 15.44 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Direct and Indirect Allorecognition

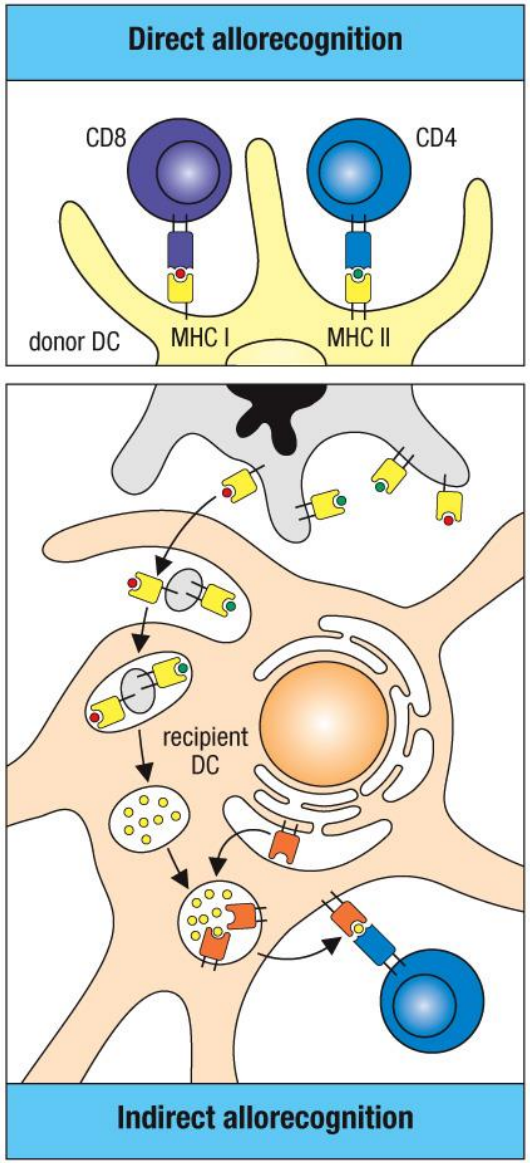
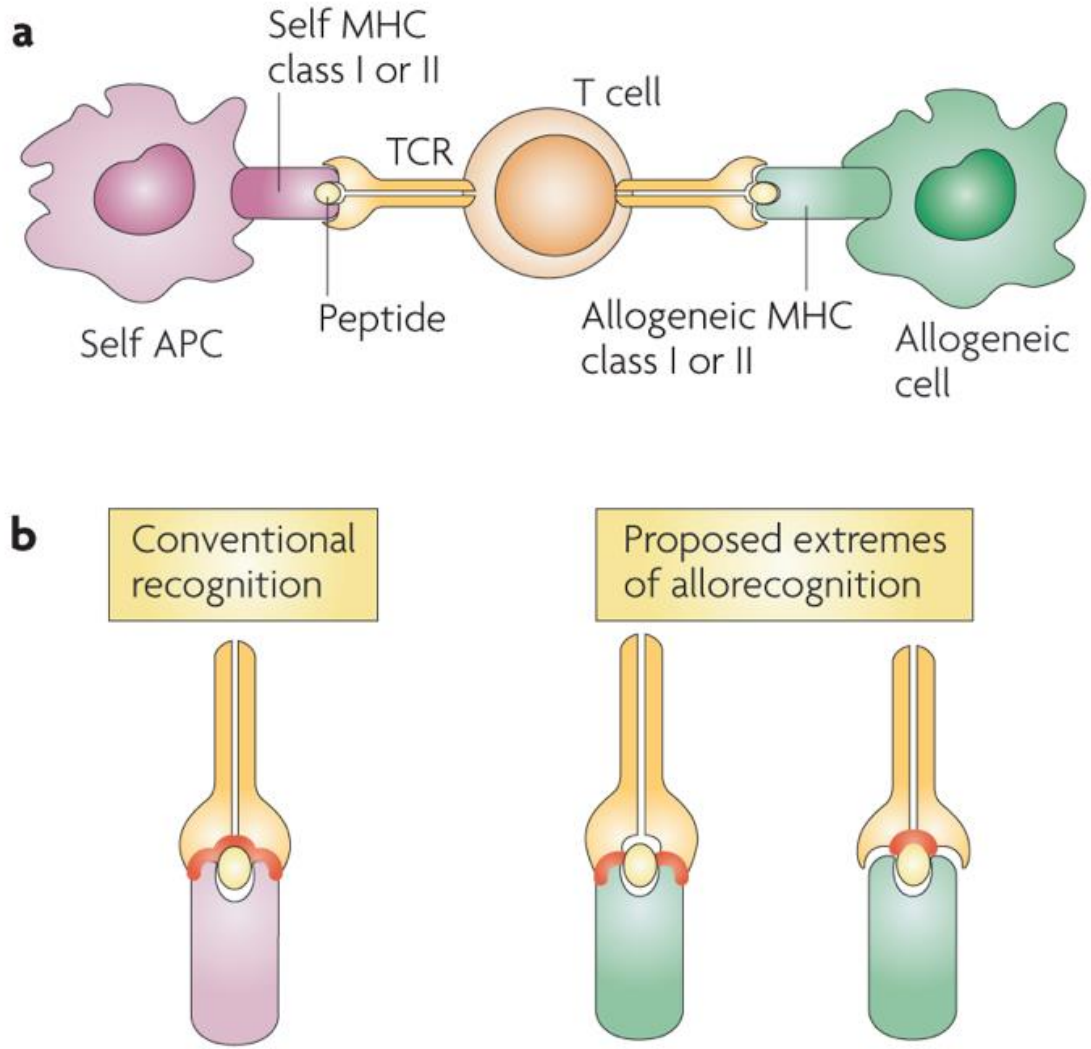


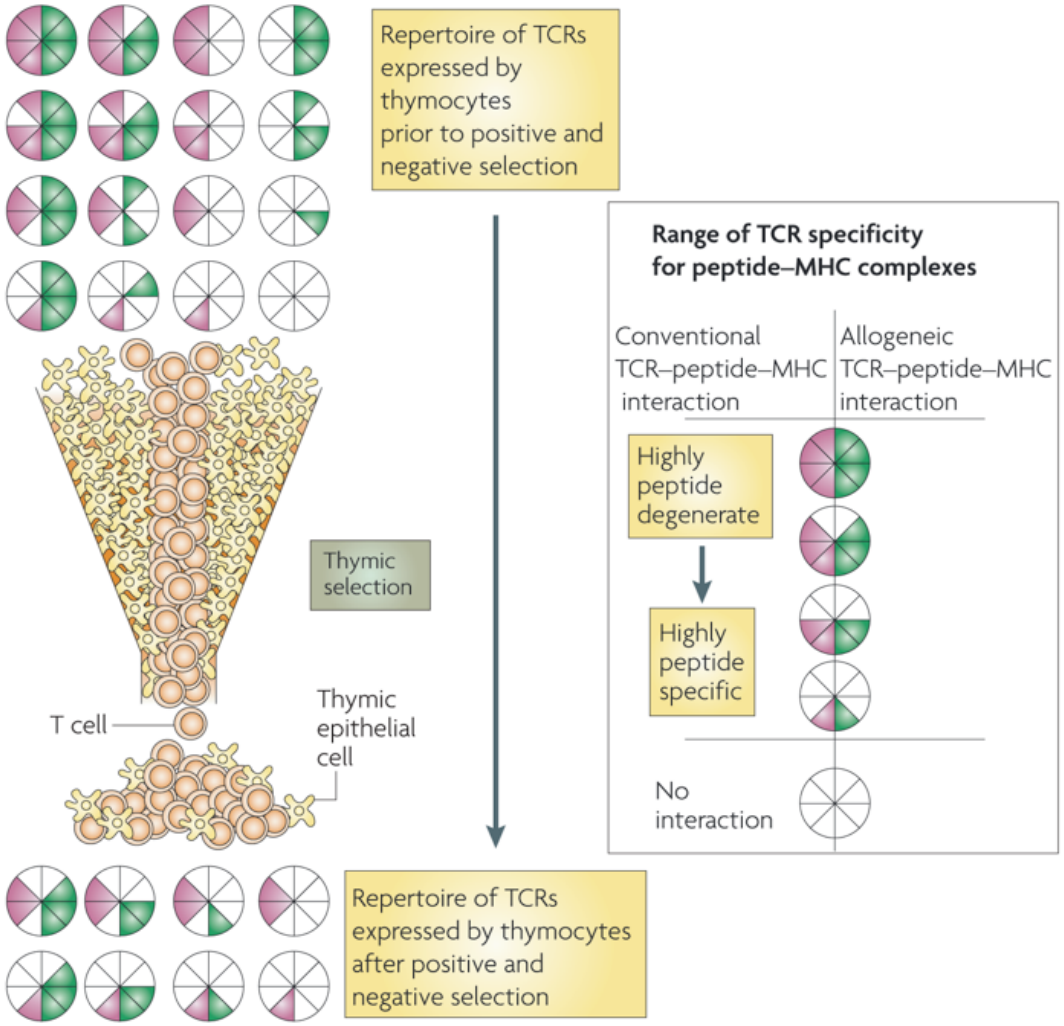
Figure 15.49 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Models of Alloreactivity



Nature Reviews Immunology. v.7, p.942 (2007)

Allo-reactive TCRs are not Eliminated During Negative Selection



Nature Reviews Immunology. v.7, p.946 (2007)

Mixed Lymphocyte Reaction Is Used to Detect Histocompatibility

Recipient lymphocytes mixed with fixed donor APC

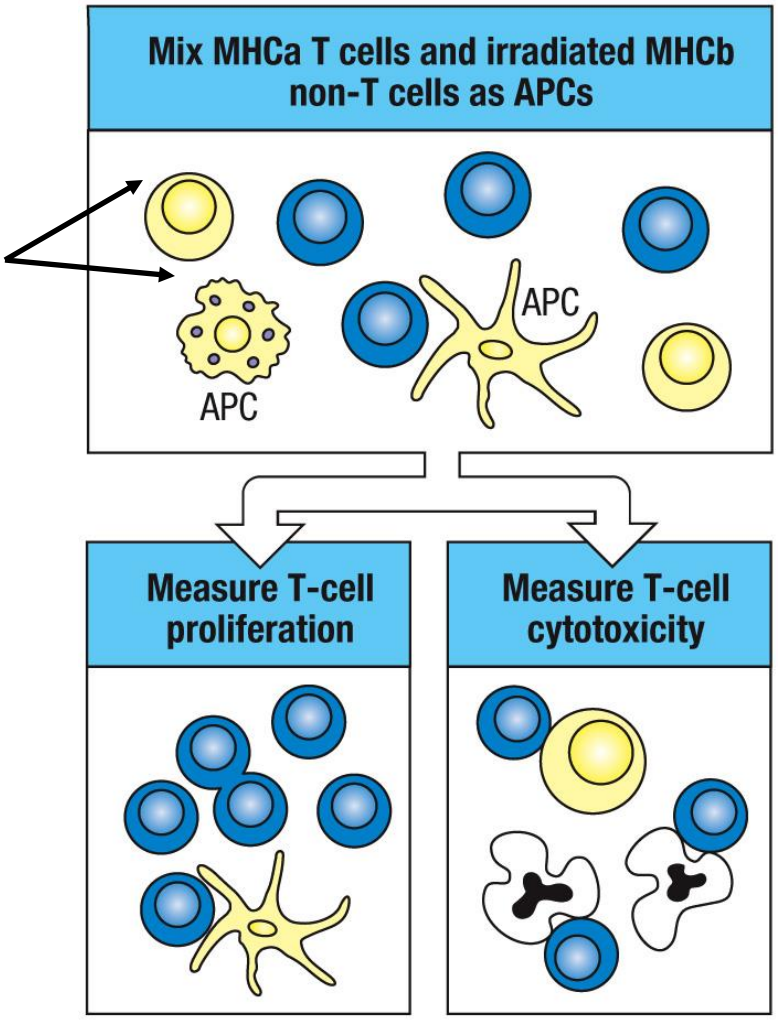


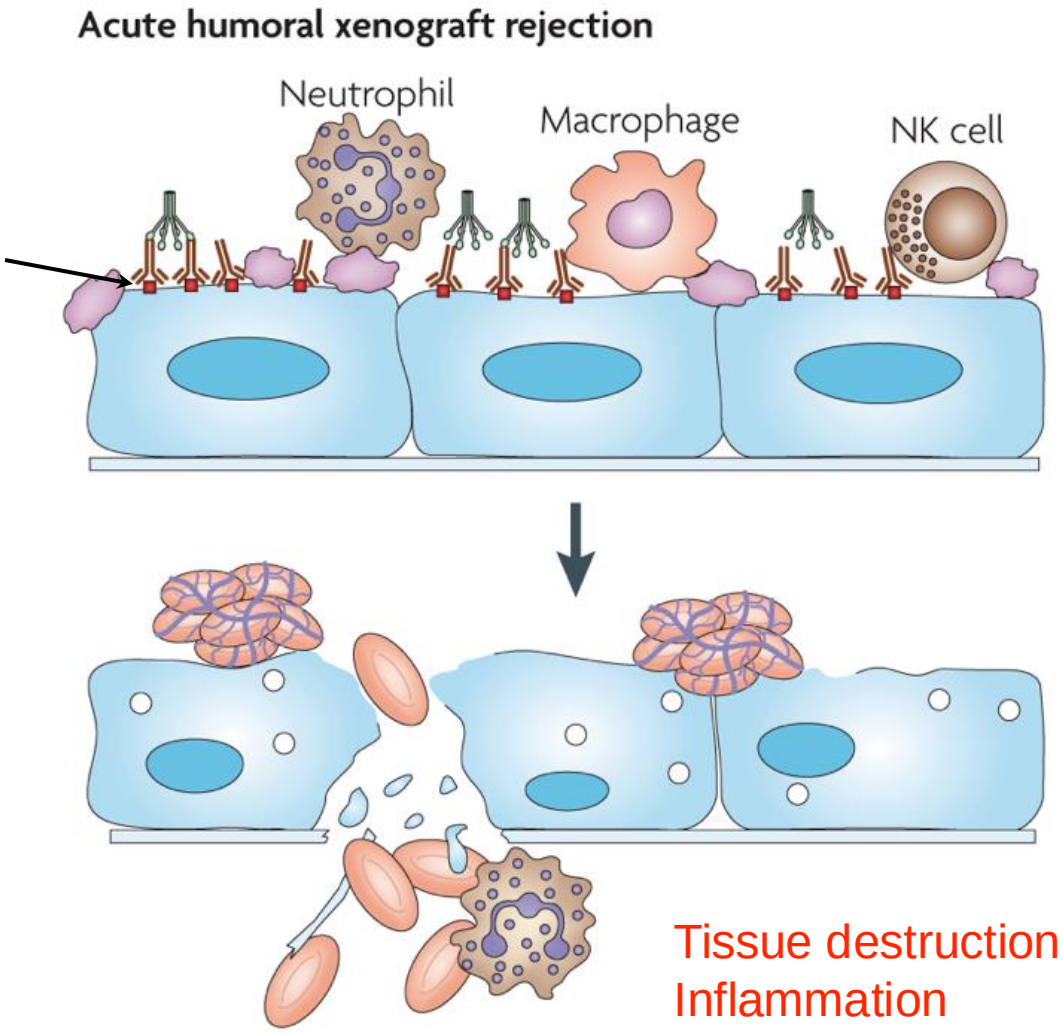
Figure 15.55 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

What indicates a better donor?

- A) minimal reaction
- B) maximal reaction

Acute Humoral Rejection

Timeframe: days-weeks



Nature Reviews Immunology. v.7, p.519 (2007)

Outline

Solid organ transplantation

- Concepts
- Hyperacute rejection, minutes-hours
- Acute rejection, days-weeks
- Chronic rejection, months-years

Bone marrow transplantation

- Graft-versus-host
- Graft-versus-tumor

Pregnancy

- Rh factor

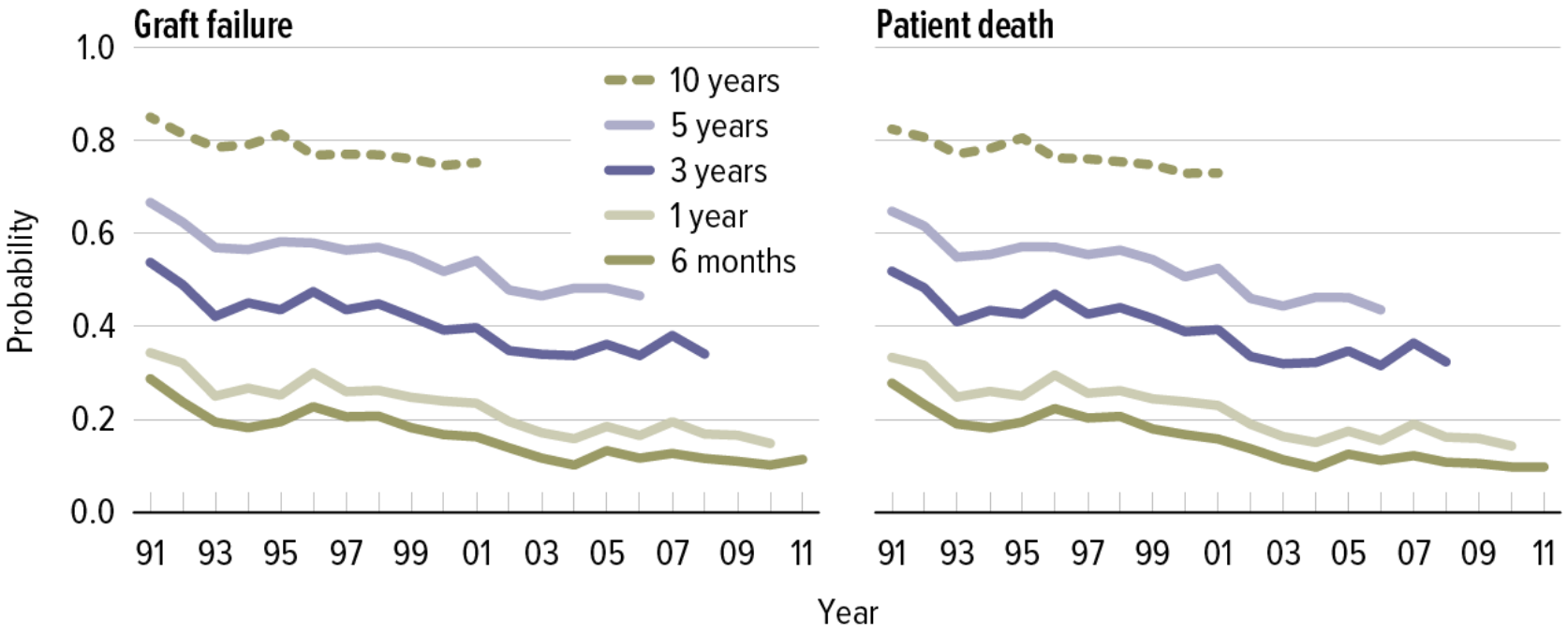
Long-term Graft Survial: A Problem of Chronic Rejection

Tissue transplanted	No. of grafts in USA (2014)*	5-year graft survival
Kidney	17,815	81.4%#
Liver	6729	68.3%
Heart	2679	74.0%
Pancreas	954	53.4%†
Lung	1949	50.6%
Intestine	139	~48.4%
Cornea	~45,000	~70%
HSC transplants	~20,000**	>80%‡

Figure 15.53 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Long-term Graft Survial: A Problem of Chronic Rejection

Lung transplantation



http://m.srtr.org/2011/chapters/lung/images/12%20LU%20s5%20fig%202-01.png

Possible Mechanisms

- Chronic Injury to the graft
- Vascular injury-hypoperfusion

  - Antibody response
  - Ischemia-reperfusion injury during surgery
  - Infections with immune suppression
  - Disease that injured the first organ

Chronic Injury to the Graft

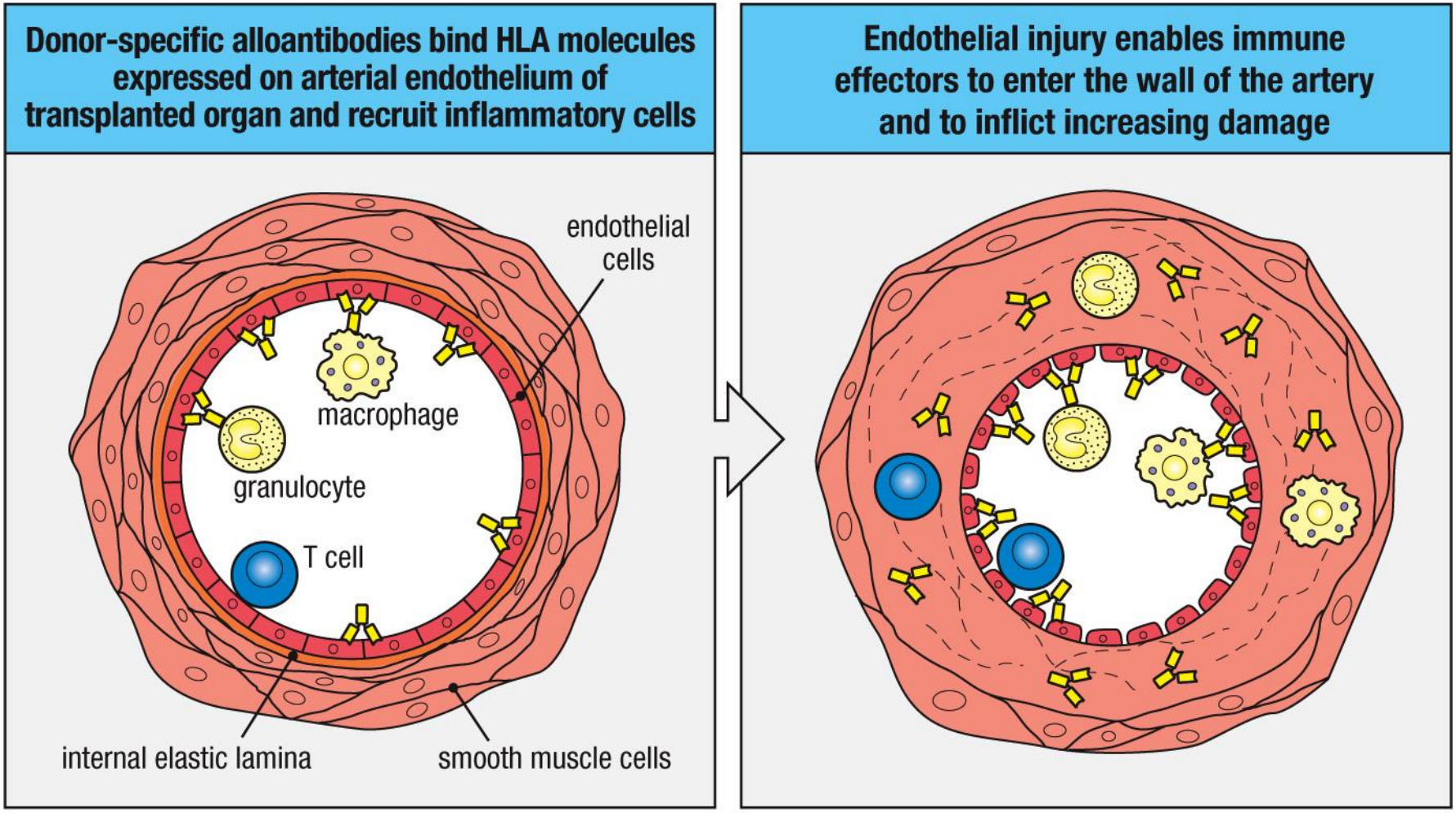


Figure 15.51 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Solid-Organ Rejection Patterns

Type	Time after transplantation	Signs and symptoms	Rapidity of onset	Immune component	Pathologic findings	Treatment	Success rate (%)
Hyperacute	<24 h	Fever, anuria	Hours	Antibody and complement	Polymorphonuclear neutrophil deposition and thrombosis	None	0
Accelerated	3-5 d	Fever, graft swelling, oliguria, tenderness	1 d	Non–complement-fixing antibody	Vascular disruption hemorrhage	Anti-lymphocyte reagents	60
Acute	6-90 d	Oliguria, salt retention, graft swelling, tenderness, sometimes fever	Days to weeks	T cells and antibody	Tubulitis, endovasculitis	Steroids, ALG, ATG, anti-CD3	60-90
Chronic	>60 d	Edema, hypertension, proteinuria, occasional hematuria	Months to years	Antibody	Vascular onion skinning	None	0

Reprinted with permission from Buckley R. Transplantation. In: Stiehm ER, editor. *Immunologic disorders in infants, children, and adults*. 5th ed. Philadelphia: WB Saunders; 2006.

J. Allergy Clin Immunol., v.125 (2010)

Solid Organ Transplantation

- To replace damaged organs
  - Trauma
  - Auto immune

- Challenge
  - Limited source of donor
  - Long-term graft rejection

Grow tissue from self cells!!!???

Outline

Solid organ transplantation
- Concepts
- Hyperacute rejection, minutes-hours
- Acute rejection, days-weeks
- Chronic rejection, months-years

Bone marrow transplantation
- Graft-versus-host
- Graft-versus-tumor

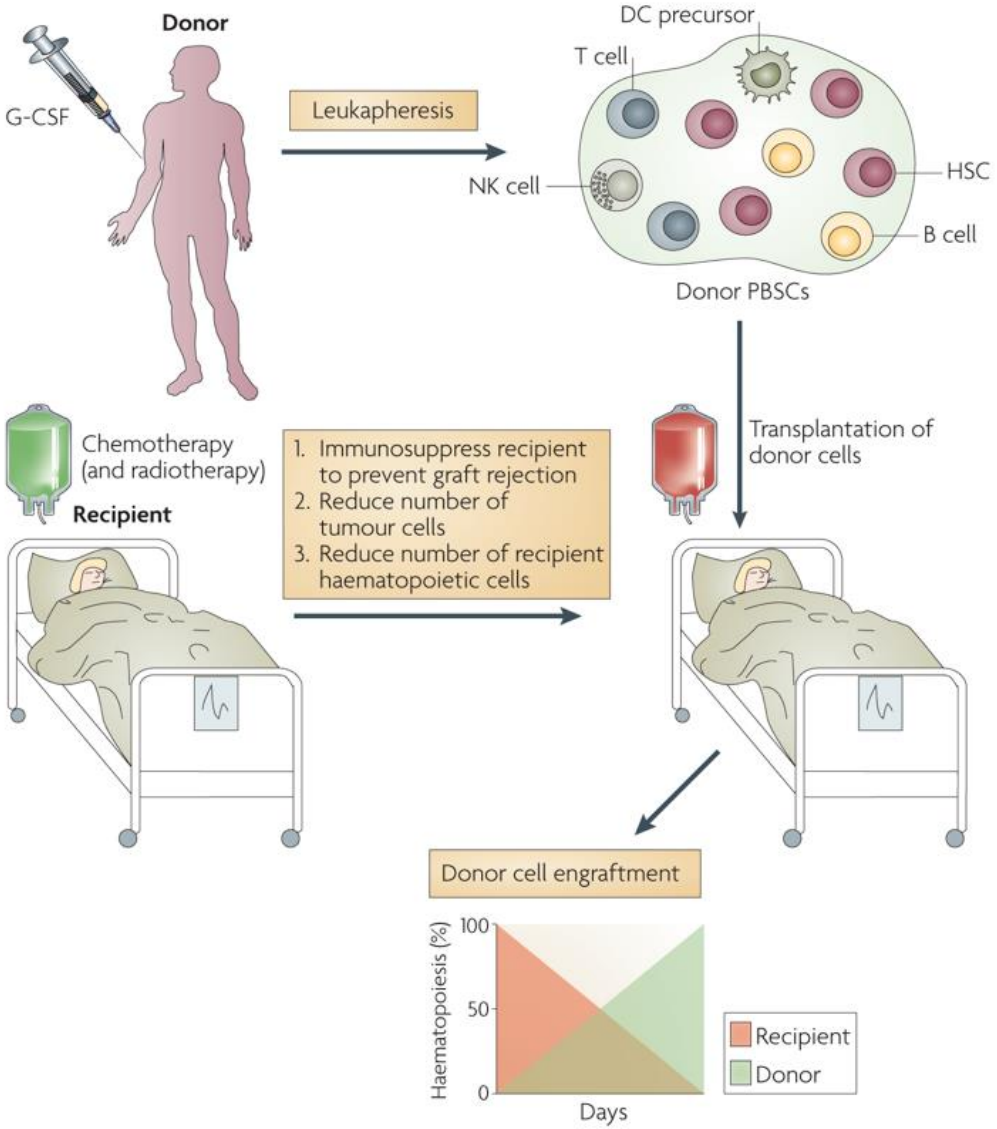
Pregnancy
- Rh factor

Bone Marrow Transplantation

Leukemias	Acute lymphoblastic leukemia Acute myelogenous leukemia Chronic lymphocytic leukemia Chronic myelogenous leukemia
Lymphomas	Non-Hodgkin lymphoma Hodgkin disease
Plasma cell disorders	Multiple myeloma and related disorders
Solid-organ neoplasias	Breast cancer, ovarian cancer, melanoma neuroblastoma, lung cancer, sarcoma
Myelodysplastic syndromes	
Severe aplastic anemia	
Autoimmune diseases	Multiple sclerosis, systemic sclerosis, systemic lupus erythematosus
Inherited erythrocyte abnormalities	Sickle cell disease, thalassemia
Inherited metabolic diseases	Mucopolysaccharidosis type I, adrenoleukodystrophy, osteopetrosis
Primary immunodeficiencies	SCID Wiskott-Aldrich syndrome CGD Leukocyte adhesion deficiency CD40 ligand deficiency X-linked lymphoproliferative disease Hemophagocytic lymphohistiocytosis

J. Allergy Clin Immunol., v.125 (2010)

Allogeneic Peripheral-Blood Stem-Cell Transplantation



Nature Reviews Immunology. v.7, p.340 (2007)

Partial MHC Match is Essential

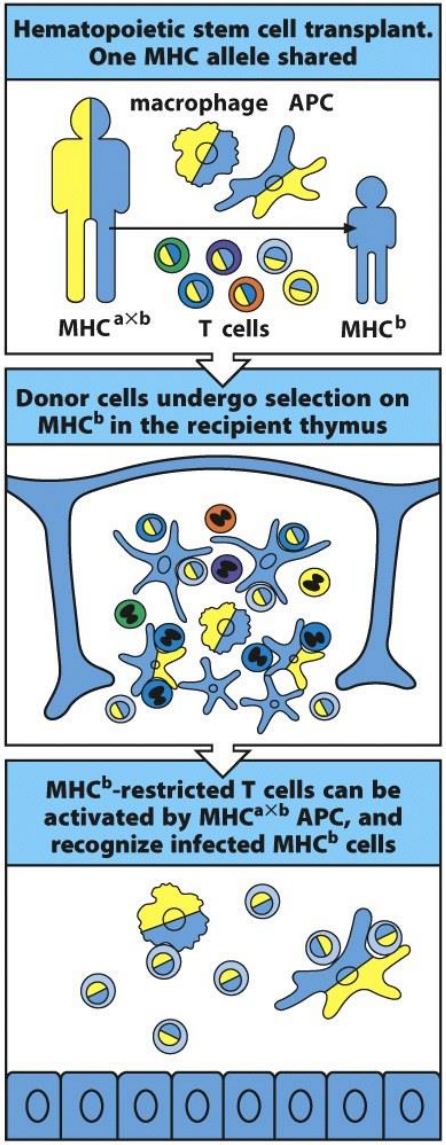


Figure 13.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Challenges

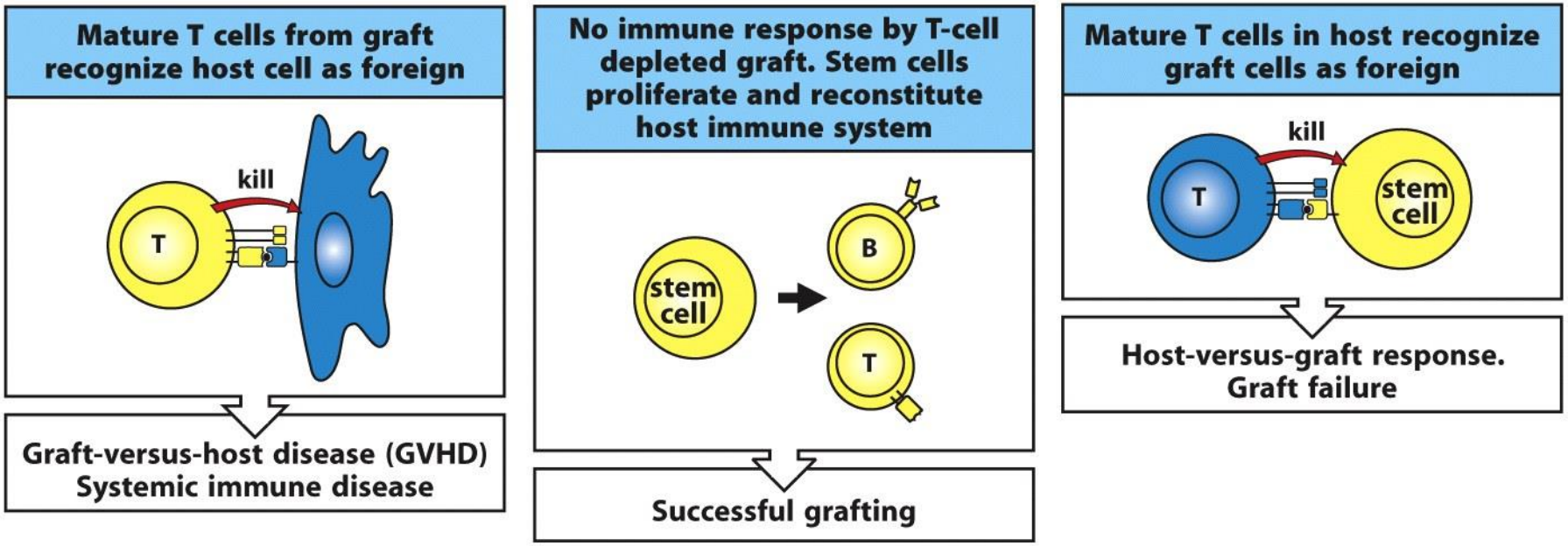


Figure 13.18 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Graft-Versus-Host Disease Is Due to the Presence of Donor T-Cells in the Graft

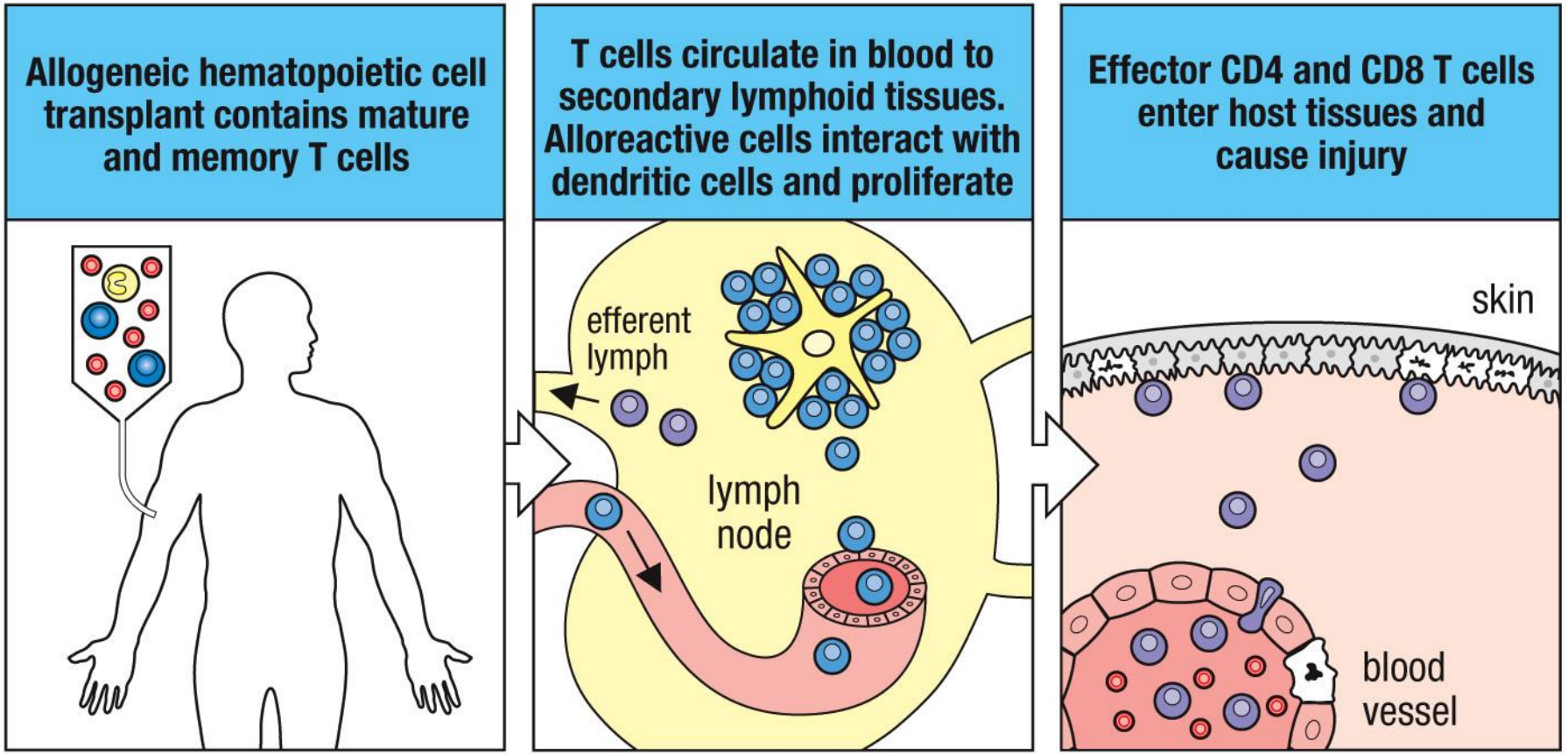


Figure 15.54 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Graft-versus-Host Disease

- Removal donor T cells
- Removal recipient dendritic cells

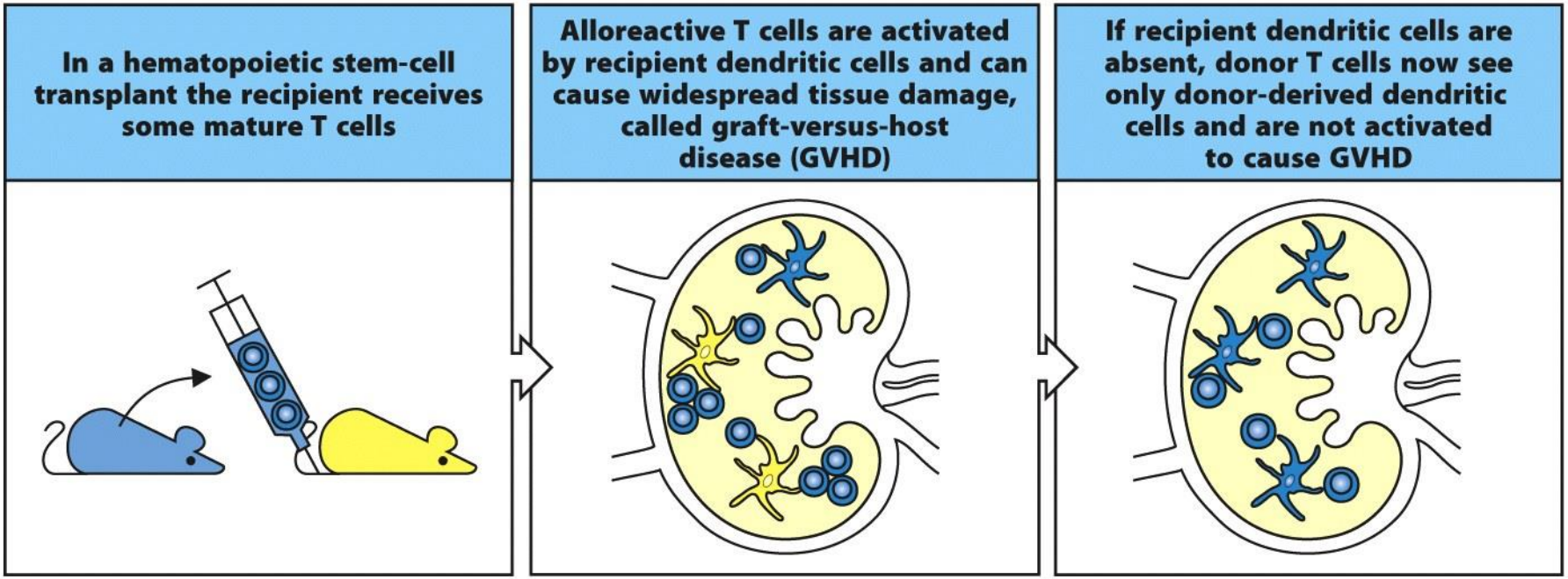
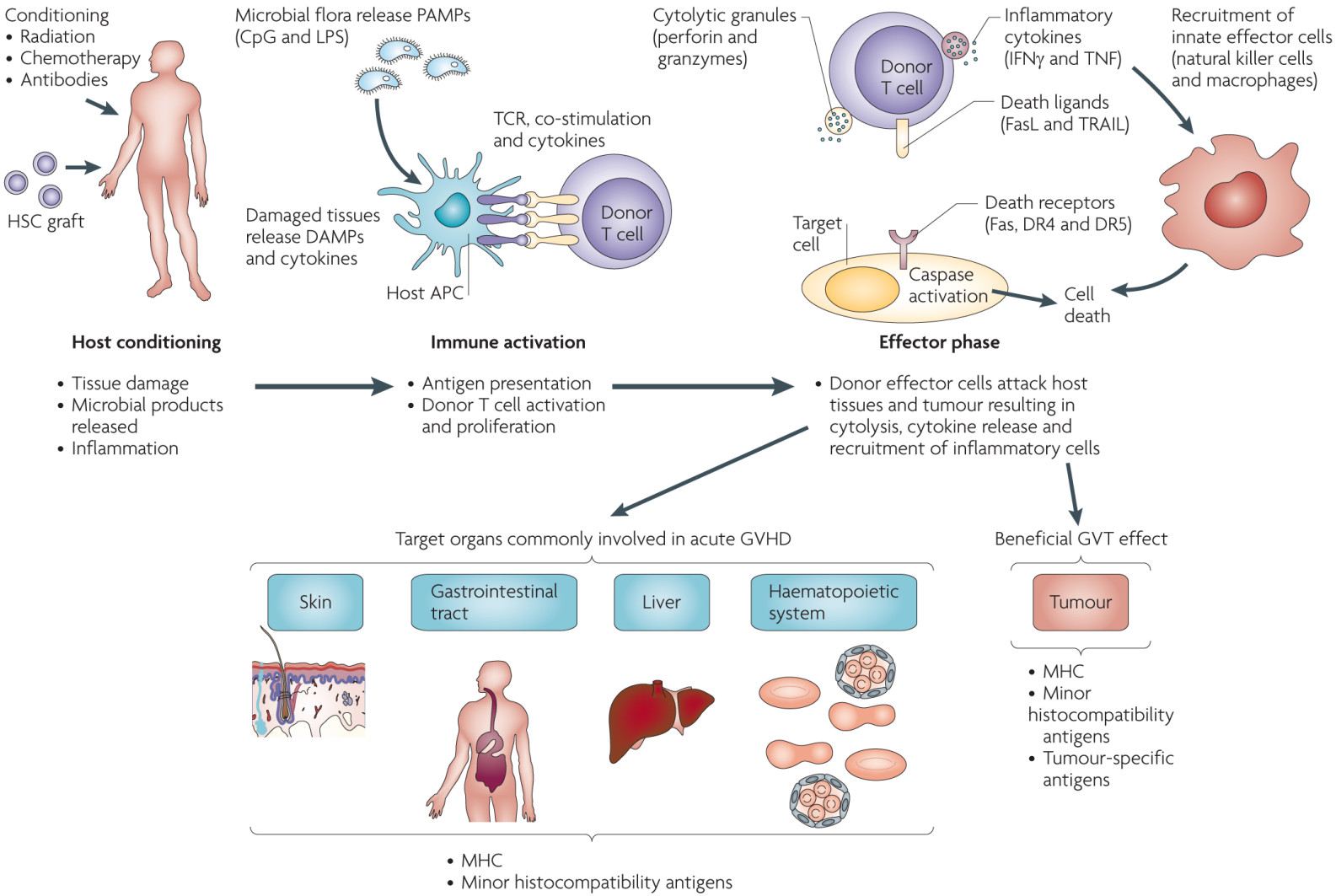


Figure 15.49 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Graft-Versus-Host and Graft-Versus-Tumor



Nature Reviews Cancer (2010)

Why is it a good idea to keep donor T cells?

- Shrinking thymus?
- To kill diseased tissue?

Question

- What mediate the immediate organ rejection?
- A) antibodies
- B) T cells
- C) both

Question

- What is the major challenge in organ transplantation?
- A) immediate rejection
- B) Acute rejection
- C) long term rejection
- D) All of the above

Outline

Solid organ transplantation
- Concepts
- Hyperacute rejection, minutes-hours
- Acute rejection, days-weeks
- Chronic rejection, months-years

Bone marrow transplantation
- Graft-versus-host
- Graft-versus-tumor

Pregnancy
- Rh factor

Fetus is an Allograft that is Tolerated

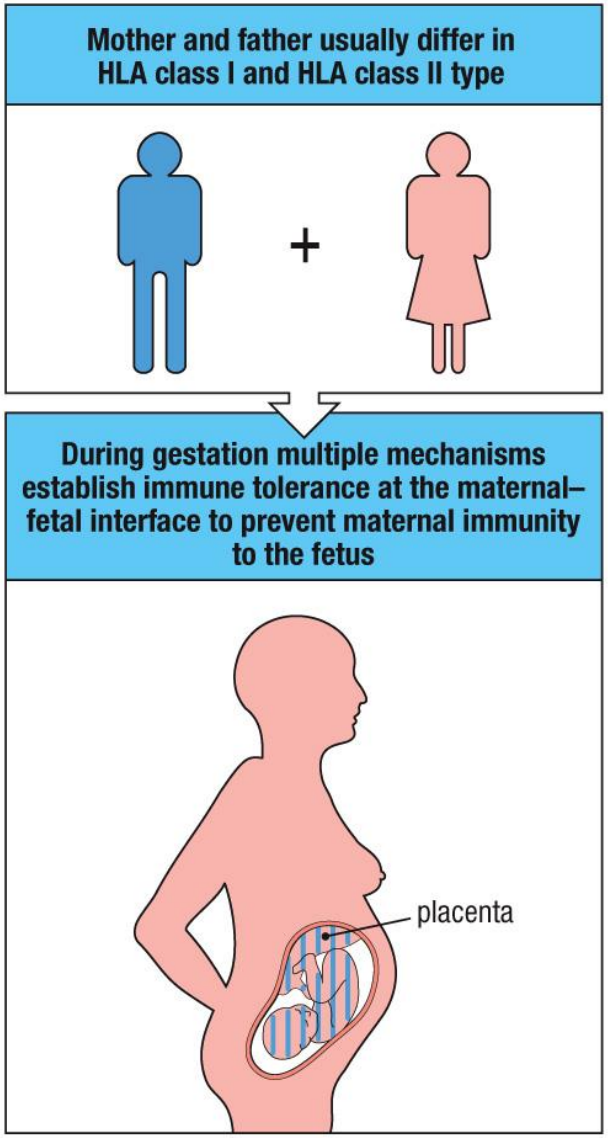


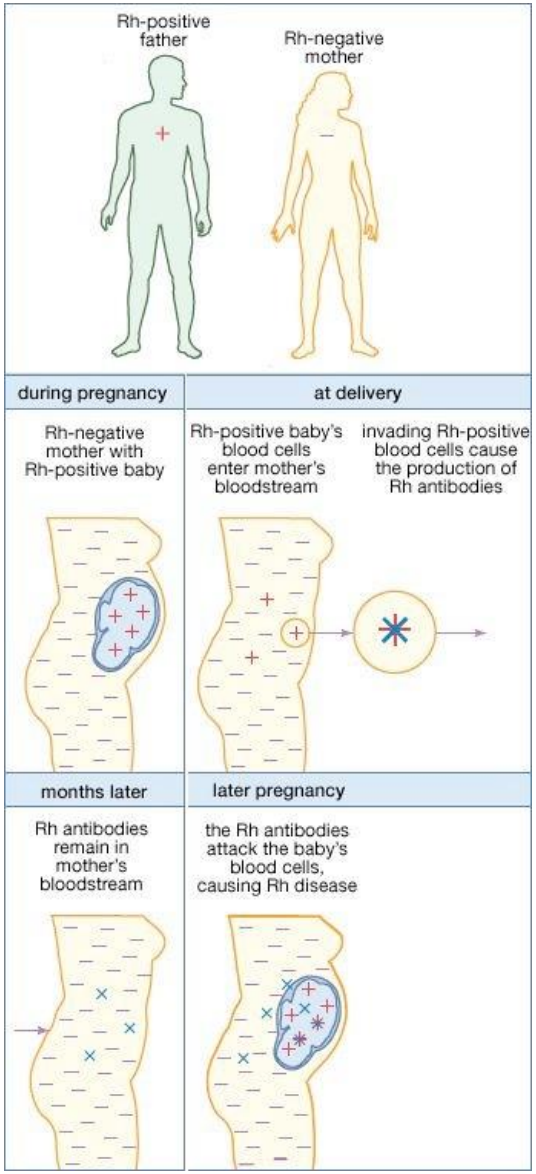
Figure 15.56 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Fetus is an Allograft that is Tolerated

- Immune privileged site
  - Separated by placenta and trophoblast
  - No MHC I and II, but HLA-G
  - Deplete tryptophan to starve T cells
  - Secrete cytokines: TGF-beta and IL-10

  - Induce transient systemic immune suppression status
    - Some fetus blood cells enter the mom

Rh Factor Is Expressed on RBCs and Can Cause Hemolytic Disease of the Newborn in an Rh- Mother



Case Study: GVHD

- Patient:
  - Aplastic anemia (bone marrow failure)
  - BMT with HLA matched sibling
  - 24 days later, rash and diarrhea
- Treatment:
  - Immune suppression
    - Corticosteroids
    - Rabbit antithymocyte globulin

Rash

Figure 11.2 Case Studies in Immunology, 6ed. (© Garland Science 2012)

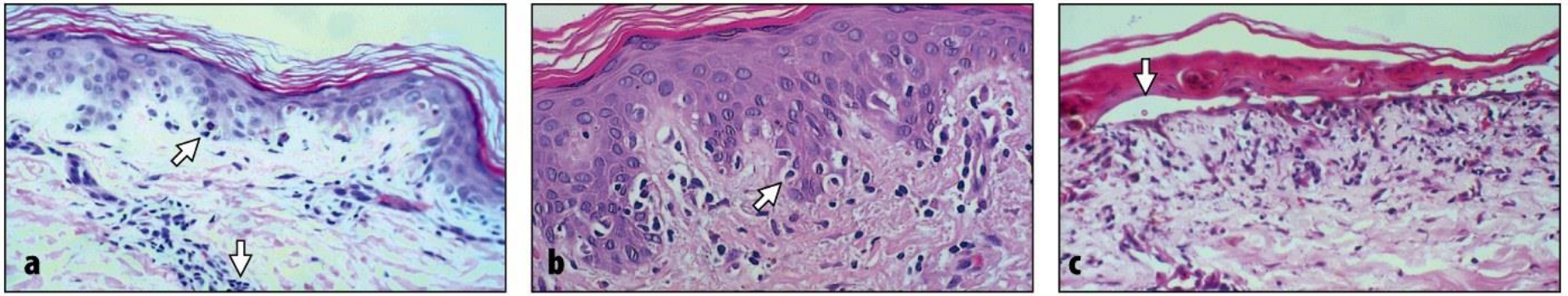


Figure 11.3 Case Studies in Immunology, 6ed. (© Garland Science 2012)

What's Wrong with the Patient?

- Donor T cells attacking recipient cells

Case Study: Hemolytic Disease of the Newborn

- Patient:
  - Fetus
  - The third child of A- mom and A+ dad
  - Hemolyze
- Treatment:
  - Transfusion with O- RBC, repeated
  - Born normal

What's Wrong with the Patient?

- Maternal IgG attack fetus RBC

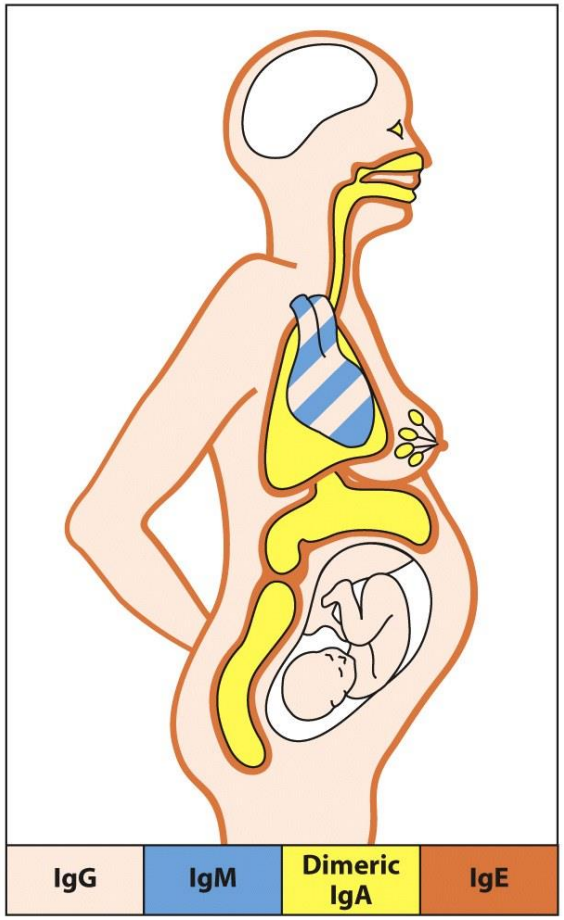


Figure 10.24 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Prevention

- Depleting Rh+ antigen during pregnancy and delivery?