Basics of Transplantation Medicine

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Organ Transplantation

- Treatment for end stage organ diseases
  - Heart, lungs, liver, kidney, pancreas, bowel
- Improves quality of life for organ recipients
- Economic benefit when compared with long term treatment

Historical overview

Prior to World War II

Improvements in surgical techniques had made transplantation possible- Rejection was insuperable.

1936 George David Snell;
compatibility of tumor cells in mice

1937 Peter Gorer and George Snells
HLA antigen system

1940 Studies on skin transplantation

1941 War adversity inspired Sir Peter Medawar to further his research in immunology

The day a bomber crashed in Oxford

Marshal "Bomber" Harris was that "It's design was so cockeyed that it always flew in the most astonishing and unusual attitude with its tail up between its ears."

After learning to fly on little biplanes like the Tiger Moth aircrew went on to train in the larger aircraft at special centres. One of these

with Florey during the morning he went to visit a friend for the afternoon but when he returned to have tea at Florey's house just after 4 pm he was told by Florey that he had just seen a bomber crash in flames in the direction of Linton Road.

Linton Road in the 1940s was a quiet North

door, number 31, occupied by Mrs C.M. Mullaly.

In the war details of military matters were subject to a reporting embargo and no details of the disaster were released to the press until May 9, when an account appeared in *The Oxford Times*. This recorded that an aircraft had

On the 50th anniversary of the war perhaps some organisation might see fit to arrange for a memorial to be erected.

The victims were: Pilot Officer (Observer) William Alexander Munro Halley, 63440, RAF, 19; Pilot Officer (Pilot) Charles Nadrin Small, 63445, RAF, 23; Sergeant (Wireless Oper-

1960 Nobel Prize awarded to Sir Peter Medawar

Historical overview

- 1954 Boston; Joseph Murray, John Merrill & Hartwell Harrison performed the first successful live human kidney transplant, between identical twins and with long-term survival
- 1960 UK's first live human kidney transplant by Sir Michael Woodruff
- 1962 Boston; Joe Murray and Roy Calne performed the first successful deceased donor kidney transplant
- 1965 The world's first transplant unit was established in Edinburgh
- 1965 Terasaki's group, in the USA proposed leucocyte HLA antigen matching as tests for donor - recipient selection
- 1967 First liver and heart transplants by Thomas Starzl & Christian Barnard
- 1978 Cyclosporine was first introduced as immunosuppressant by Sir Roy Calne

Transplants are generally “foreign”

- **Autografts -** skin grafts from one site to another on the same individual
- **Isografts or syngeneic transplants -** between monozygotic twins
- **Allograft or allogeneic transplants -** between two genetically distinct individuals
- **Xenografts (foreign) -** grafts obtained from a different species from the recipient

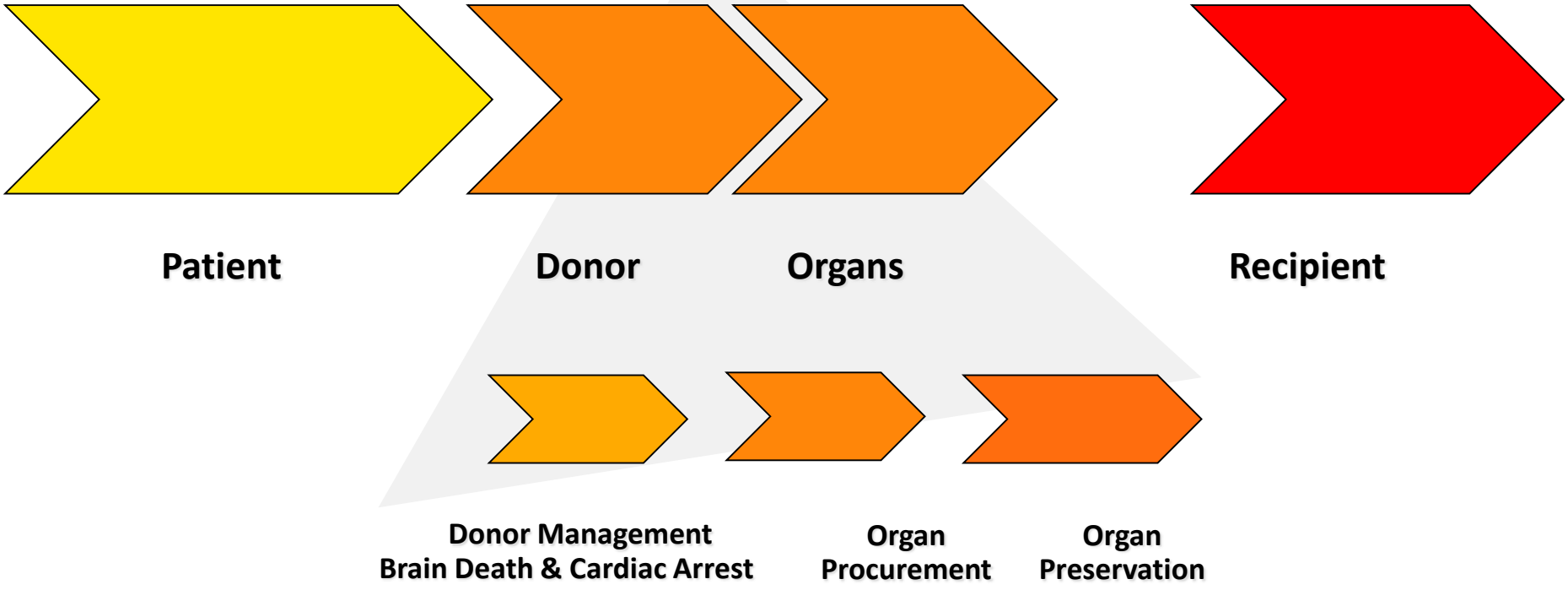
Donor types

- Donation after Brain Death (DBD):
  Cerebral injury followed by herniation of brain stem

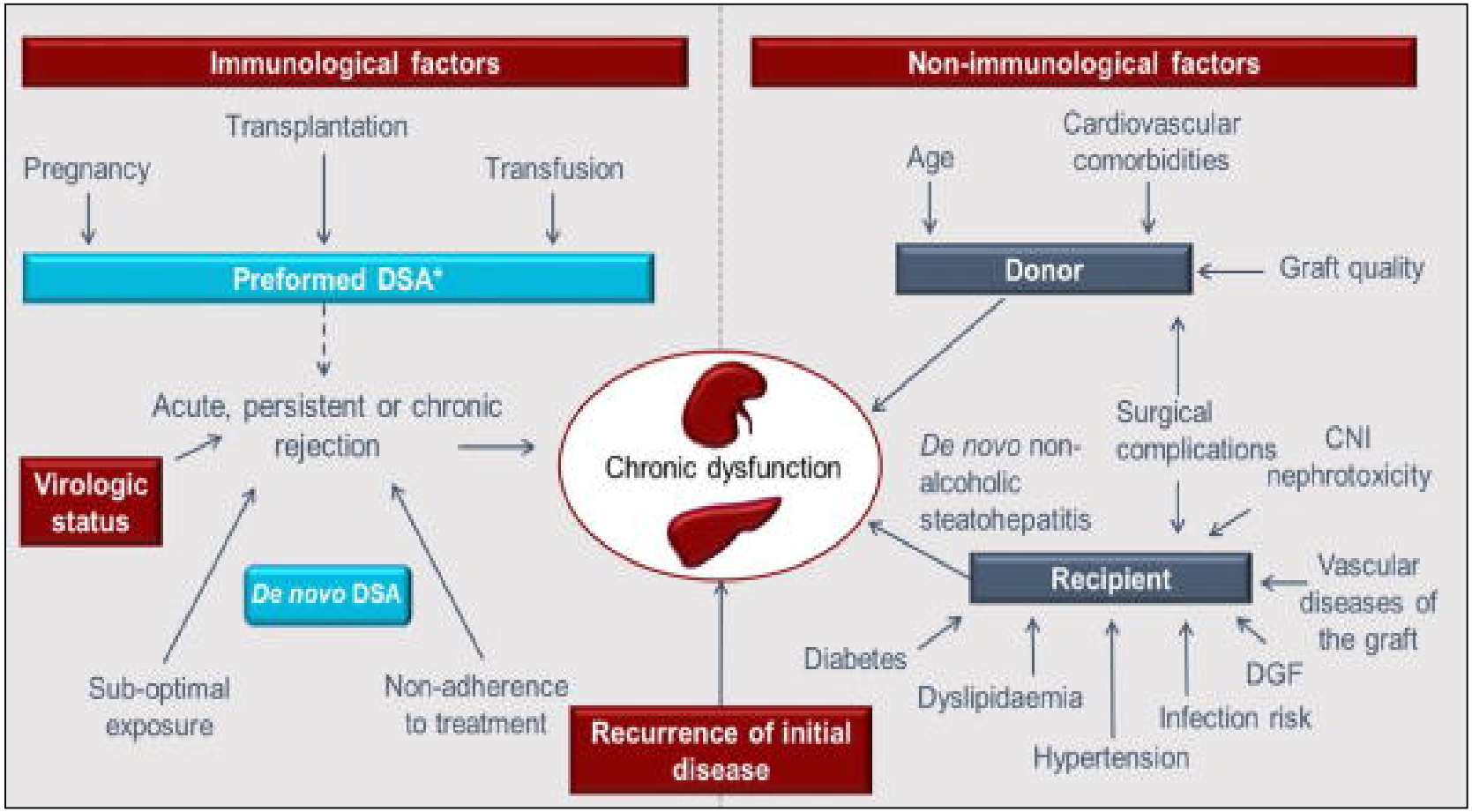
- Donation after Circulatory Arrest (DCD):
  Futile medical treatment and withdrawal of support

- Living donors (LD):
  Relatives, spouses, friends, altruistic donors

Organ Donation Preservation Transplantation Process



Organ transplantation
immunological vs non immunological factors



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Impact of immunological factors on graft survival

Immune rejection of transplants

- **Hyperacute rejection**
- **Acute rejection**
- **Chronic rejection**

Hyperacute graft rejection

- **Pre-existing antibodies against blood group & HLA antigens expressed on the graft lead to rapid organ rejection**
- **ABO antigens are expressed on all tissues including vascular endothelial cells**
- **HLA class I molecules are expressed on all cells**
- **Occurs in minutes and is complement dependent**

Hyperacute rejection
Pre-existing antibodies bind to donor ABO antigens

Inflammatory response elicits from pre existing Abs in the recipient that bind to donor ABO antigens causing occlusion of blood vessels

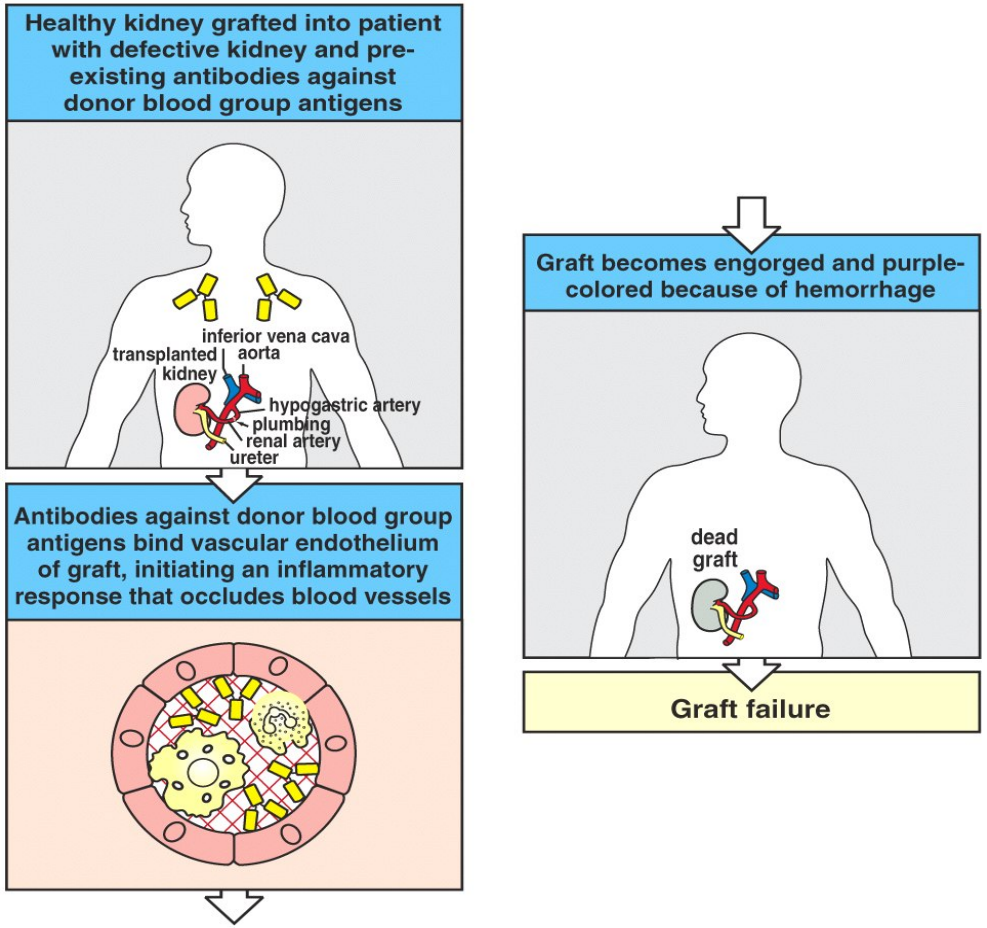


Figure 12-14 The Immune System, 2/e (© Garland Science 2005)

Hyperacute graft rejection

- **Hyperacute rejection leads to graft loss within minutes**
- **ABO-matching and ‘cross-matching’ donor and recipient can prevent hyperacute rejection**
- **Cross-matching determines whether the recipient has pre-existing antibodies against donor leukocytes**

Acute rejection

Acute skin graft rejection mediated by T cells

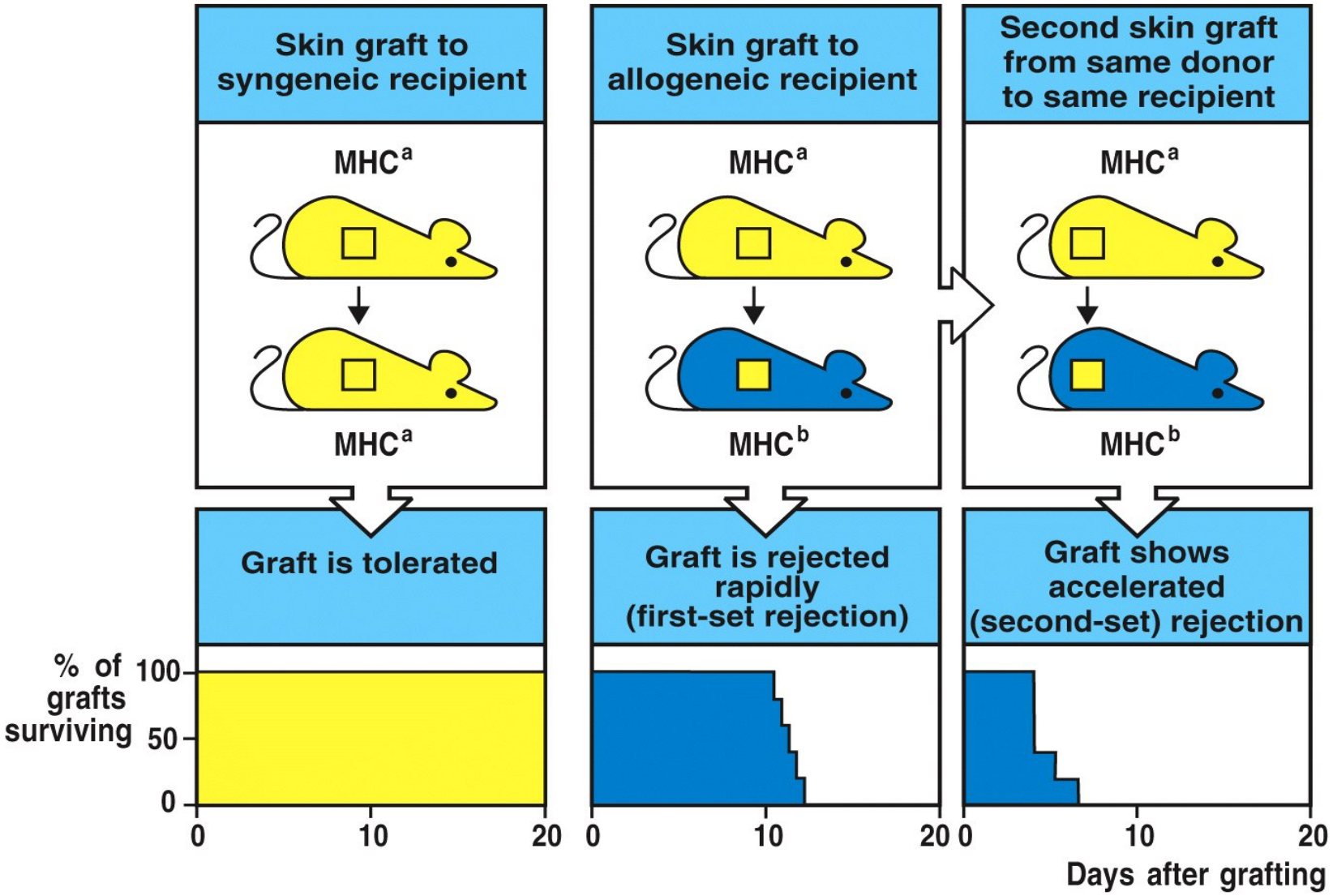


Figure 13-35 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Acute rejection of graft with HLA mismatch

- Alloreactive T cells cause rejection

- Inflamed Graft
  - swollen
  - necrosis
  - Pathology develops over days

- Therapautic options
  - Immunosupressive regime aims to reduce T cell activation

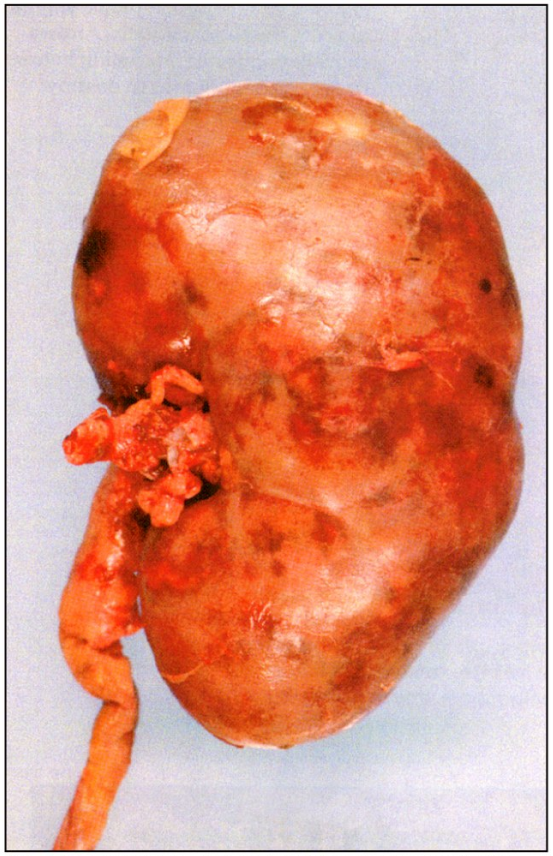


Figure 12-17 The Immune System, 2/e (© Garland Science 2005)

Acute rejection
Direct pathway of allorecognition

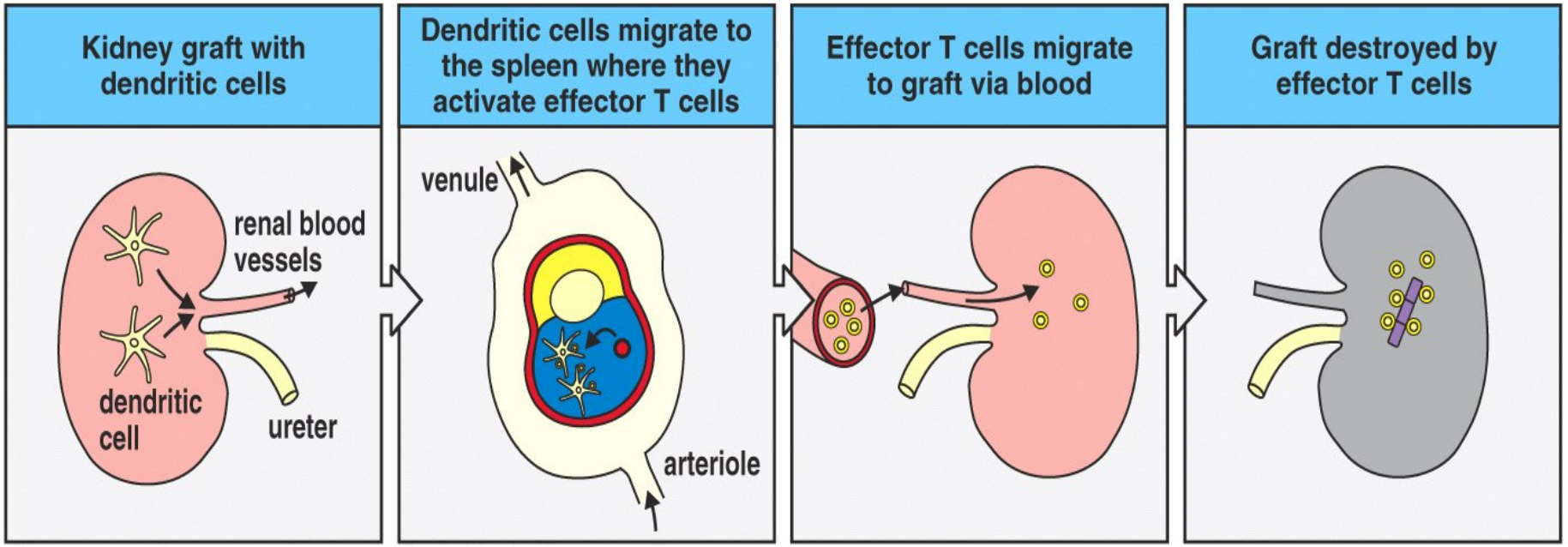


Figure 12-18 The Immune System, 2/e (© Garland Science 2005)

Donor dendritic cells are recognised by recipient T cells

Acute rejection

- Recipient T cell recognition of donor DCs

- T cells activation upon recognition of allogeneic HLA class I or class II (direct allorecognistion)

- Effector CD8 T cells proliferation

- Effector T_H1 cells activate macrophages to produce inflammatory cytokines (IL-1, IL-6, TNFa)

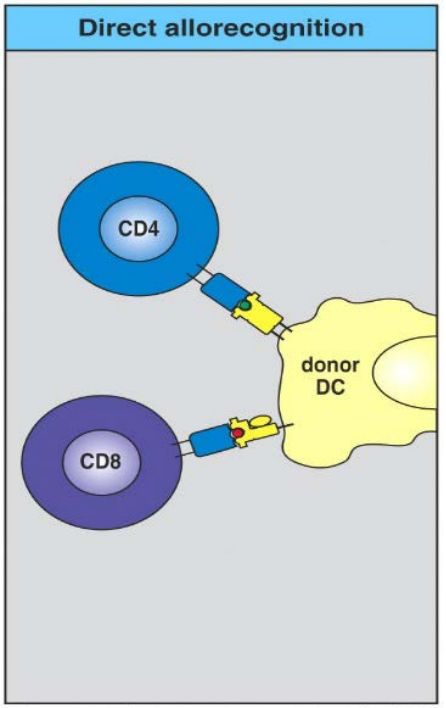


Figure 12-19 The Immune System, 2/e (© Garland Scien

Acute rejection

Direct & Indirect allorecognition of HLA antigens

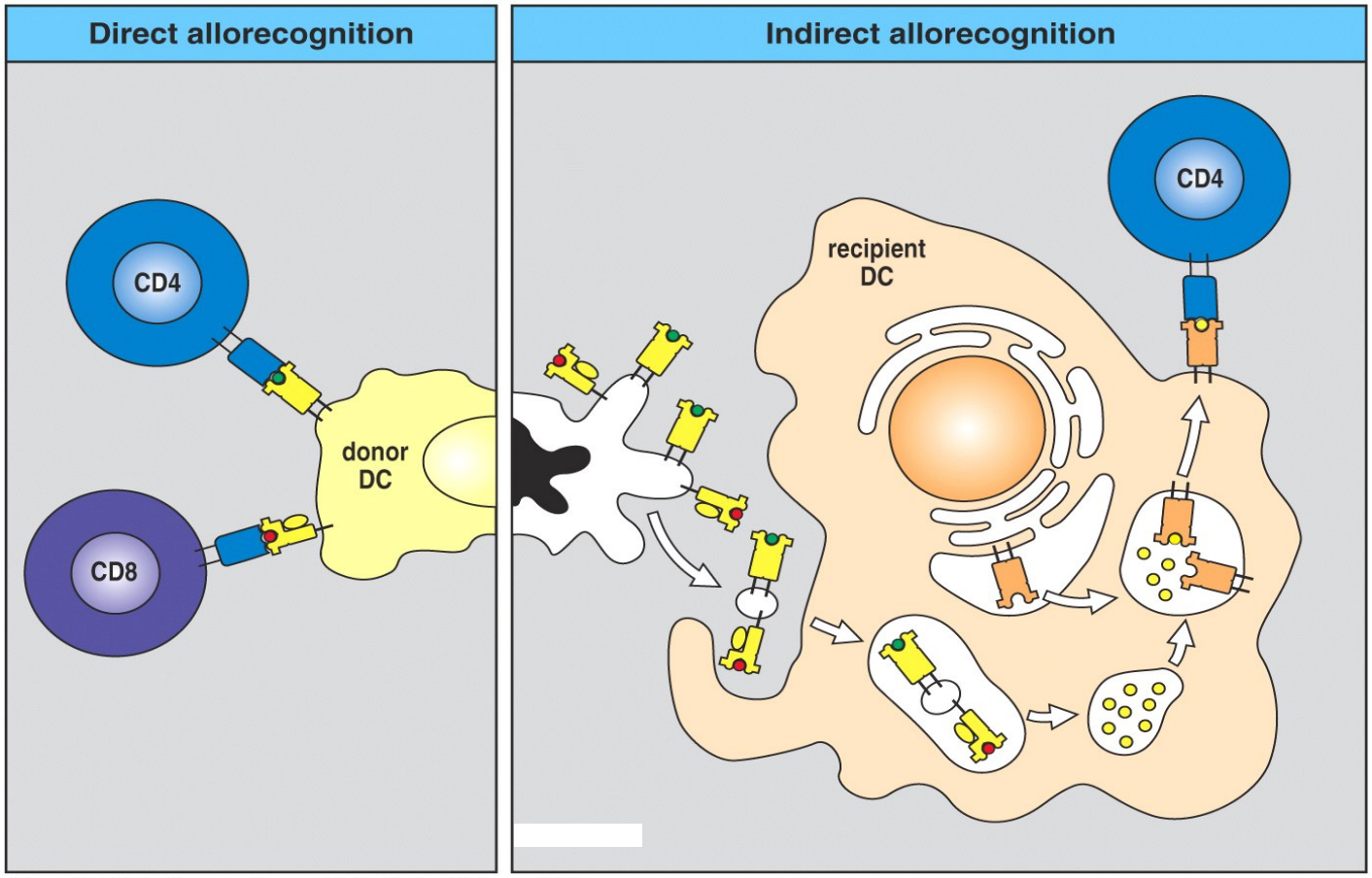


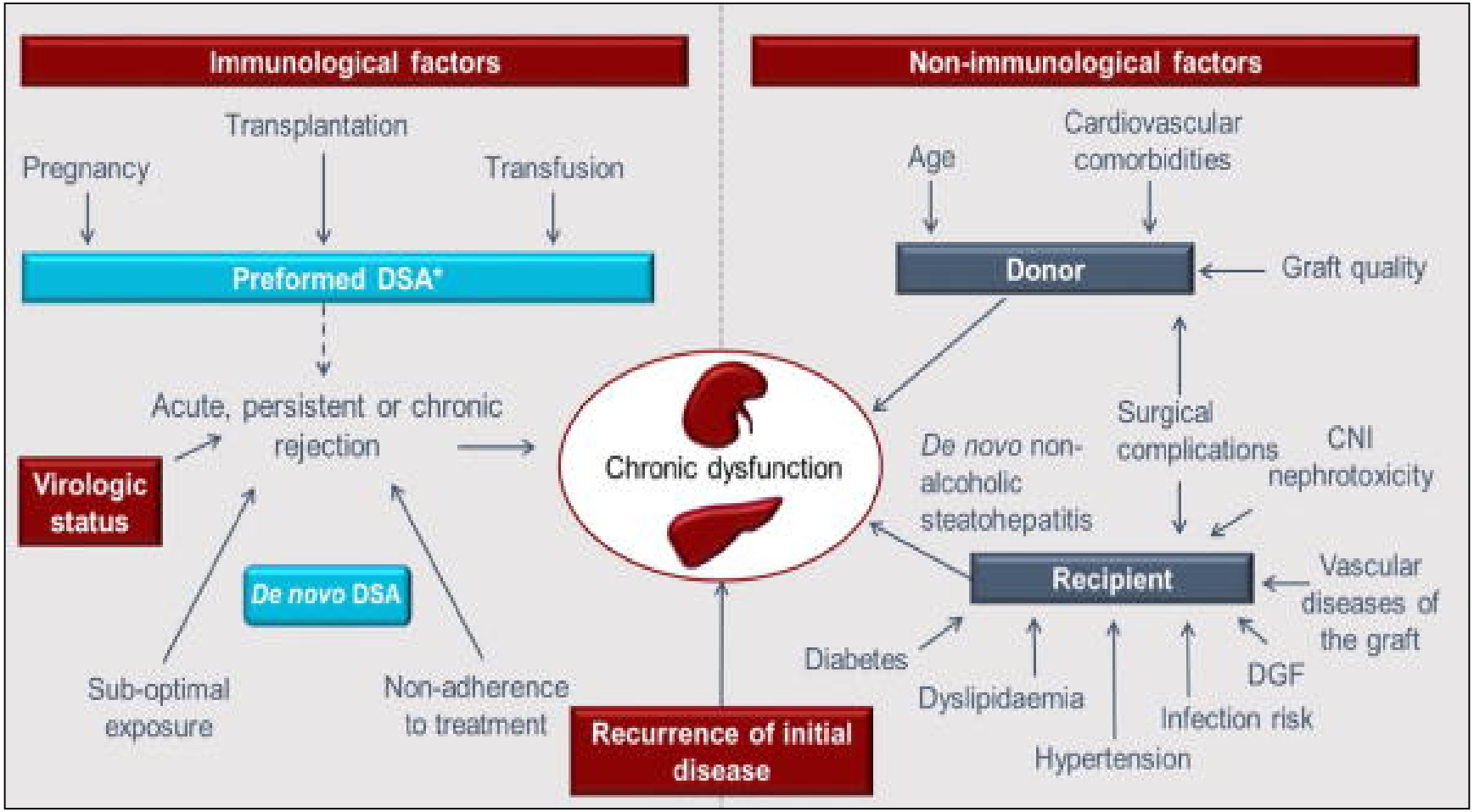
Figure 12-19 The Immune System, 2/e (© Garland Science 2005)

Indirect

Graft derived proteins are taken up and processed by the recipient DC and are presented by self (recipient) MHC class I or II molecules.

Non immunological triggers for organ failure and graft dysfunction

Challenges in solid organ transplantation immunological vs non immunological factors



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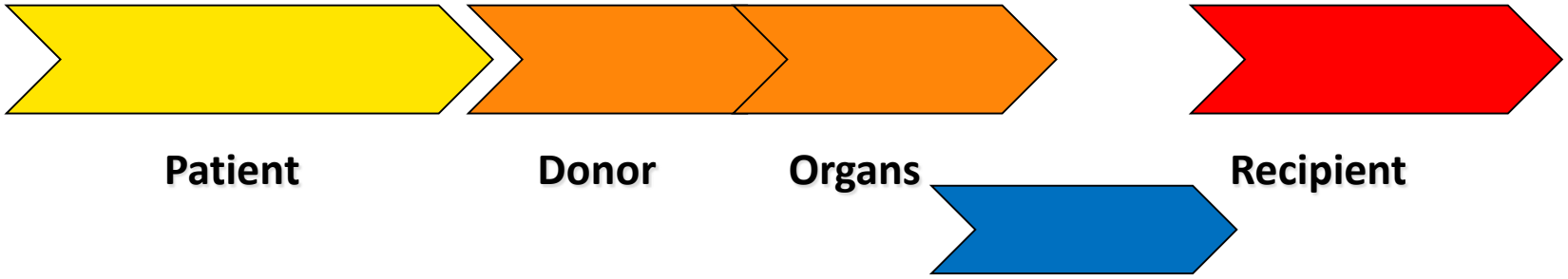
Non-immunological factors

- Donor age- Independent predictor of transplantation outcomes

- Hypothermic preservation- the period between organ procurement and graft reperfusion in the recipient; **the main cause of ischaemia reperfusion injury**



Non-immunological factors

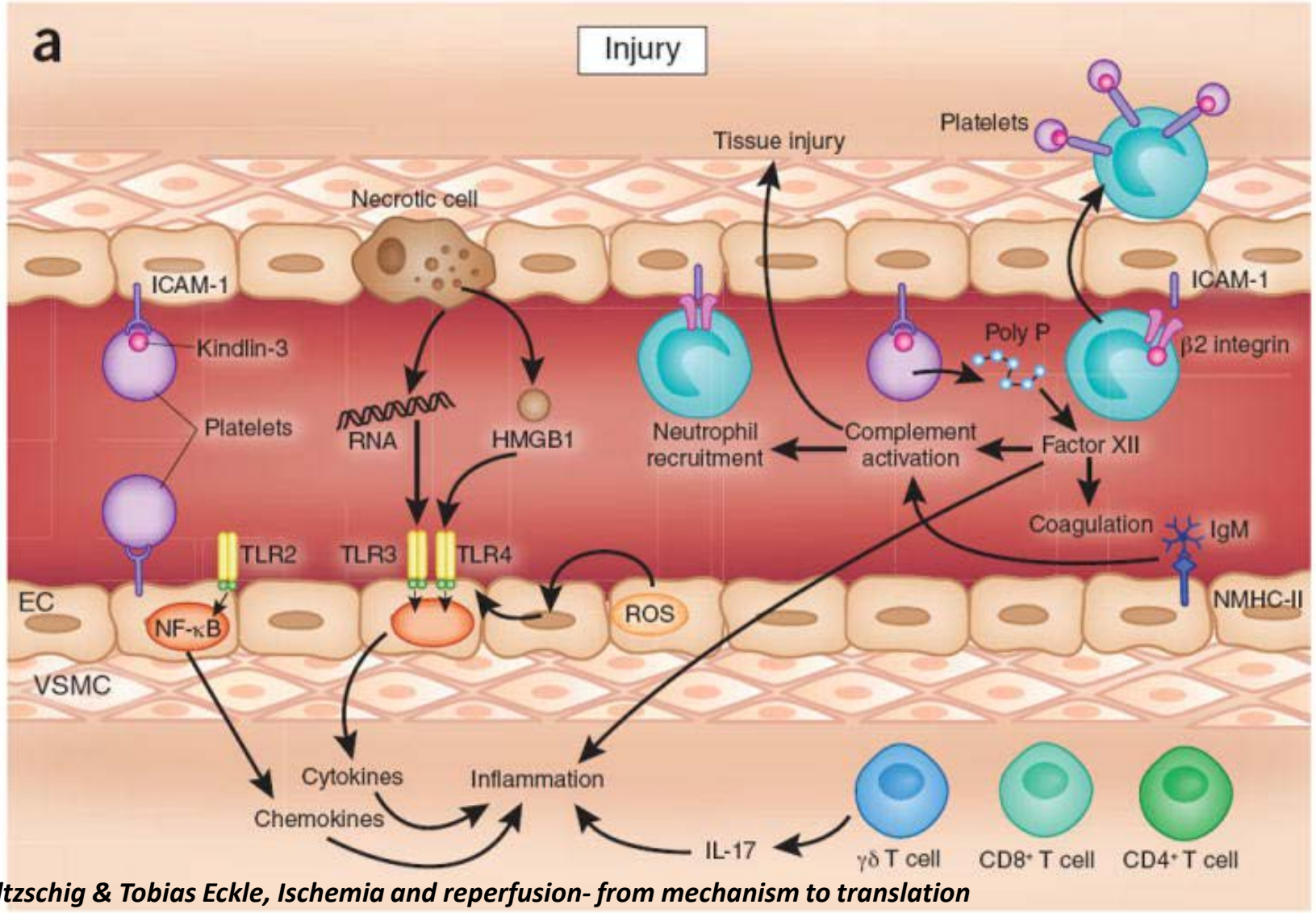
- Ischaemia and reperfusion is a pathological condition characterized by an initial restriction of blood supply to an organ followed by the sub- sequent restoration of perfusion and reoxygenation.

- Limited or no oxygen delivery in the organ dysregulates metabolic activity on the cellular level
  - Tissue hypoxia
  - Endothelia activation
  - Production of reactive oxygen species

- Restoration of oxygenation promotes tissue injury and extensive inflammatory response

Non immunological triggers for graft dysfunction

Ischemia and reperfusion triggers a pathological activation of the immune system



H K Eltzschig & Tobias Eckle, Ischemia and reperfusion- from mechanism to translation
Nat Med. 2011 Nov 7; 17(11)

Chronic graft rejection

- Reflects a slow loss of graft function
- Interplay of immunological and non immunological factors
- Donor organ quality has a long term impact on the transplant
- Correlates with the presence of antibodies
- Long term impact of ischemia-reperfusion injury

Conclusions

- Organ transplantation is a life saving and life transforming treatment of end stage disease
- Transplantation outcomes depend on a range of factors related to donor, graft and recipient
- Great achievements in Transplantation Medicine the last few decades have improved allograft function for organ recipients