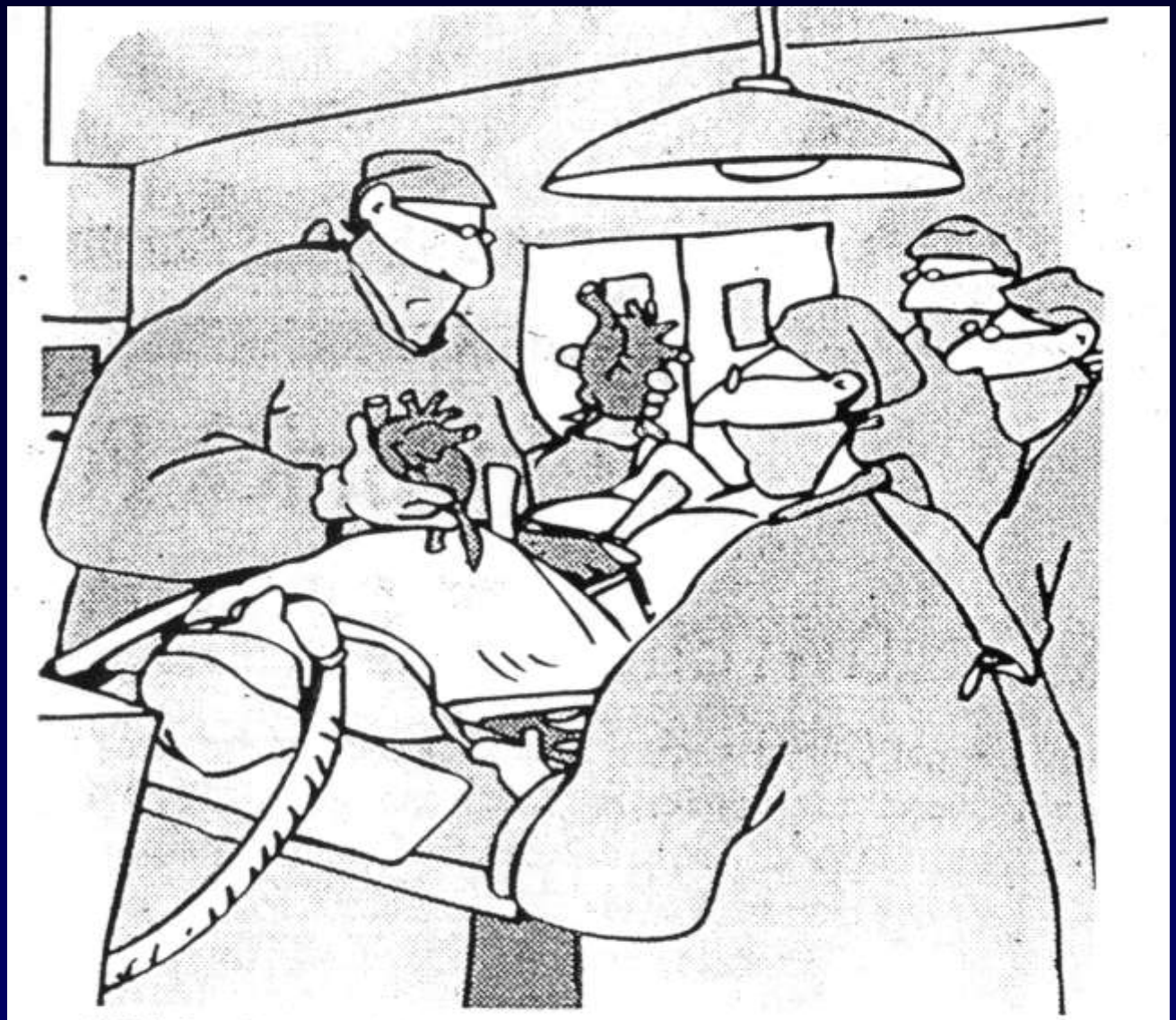
Transplantation Immunology

Outline

- Definitions
- Transplantation antigens
- Antigen presentation and recognition
- Mechanisms of transplant rejection
- Effectors of graft rejection
- Immunosuppressive drugs
- **Why does mother not reject fetus?**



"OK, the old one's in my right hand,
the donor's in my left. Right?"

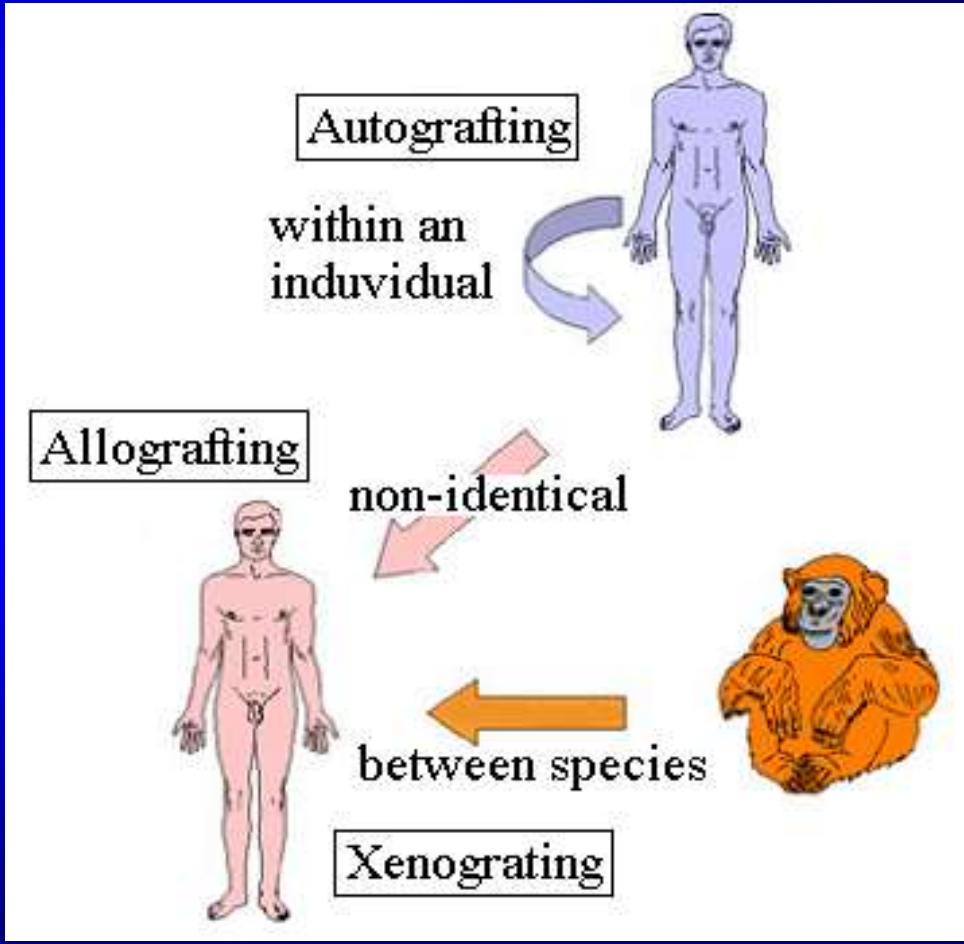
Transplantation

- **Graft or Transplant: Transfer of living cells, tissues and organs from one part of the body to another or from one individual to another.**

Methods of Transplantation:

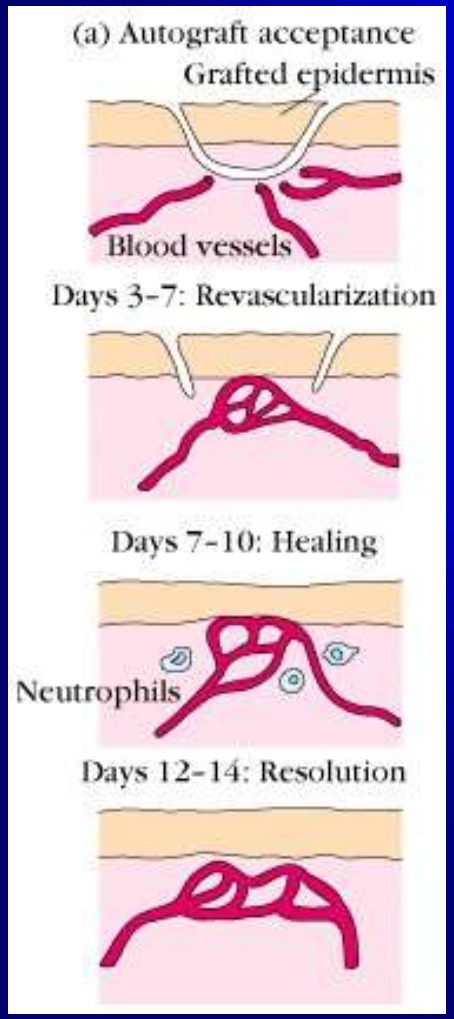
<u>May take place between:</u>

- different parts of the same organism (autografting)
- different organisms of the same species (allografting)
- different species (xenografting)



Methods of Transplantation:

Autografting

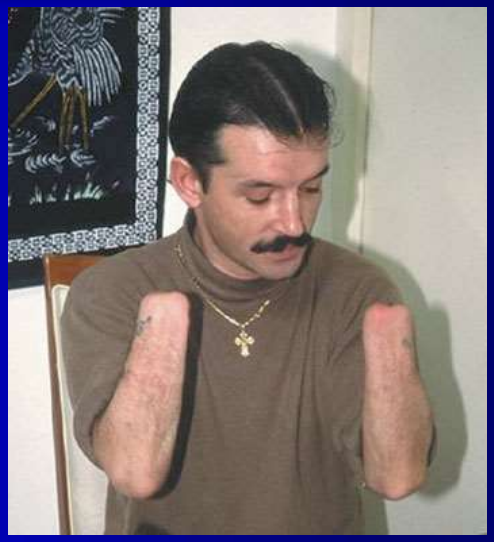


- The transfer of self tissue from one body site to another in the same individual
- Due to the genetic homology of the tissue, the immune system does not respond to it
- Use: synthetic implantation
  - skin grafts
  - bone marrow transplantation
  - hair

Methods of Transplantation:

Allografting

Definition: The transfer of organs or tissue from human to human.



- As there are more and more people every year waiting for donor organs and tissues, allografting transplantation has become quite common.
- Allografting transplantation has many applications.

Methods of Transplantation:

Xenografting

Definition: Xenotransplantation – the transfer of tissue from one species to another

Usually refers to the implantation of animal tissue in humans

- provides a new source of organs for humans
- many different types of tissue can be transplanted:

  e.g. heart, kidney, liver or lung

General information

Immune system rejection

Often a transplanted organ is not identified by the immune system as the tissue of the organism

→ It can be attacked and destroyed.

Against this effect, the patient has to swallow Immunesuppressive which cause symptoms like suffering from AIDS.

In 15-20 minutes the organ dies, unable to withstand the immune system attack.

Rejection of a heart

Transplantation antigens (1)

Major Histocompatibility Complex (MHC):

- gene complex whose alleles encode polymorphic cell surface glycoproteins involved in antigen recognition and presentation
- MHC-matching between transplant donor and recipient greatly reduces likelihood of rejection
- nomenclature
  - HLA: human leukocyte antigen
  - SLA: porcine leukocyte antigen
  - H-2: mouse MHC
  - RT1: rat MHC

Transplantation antigens

Major Histocompatibility Complex (MHC):

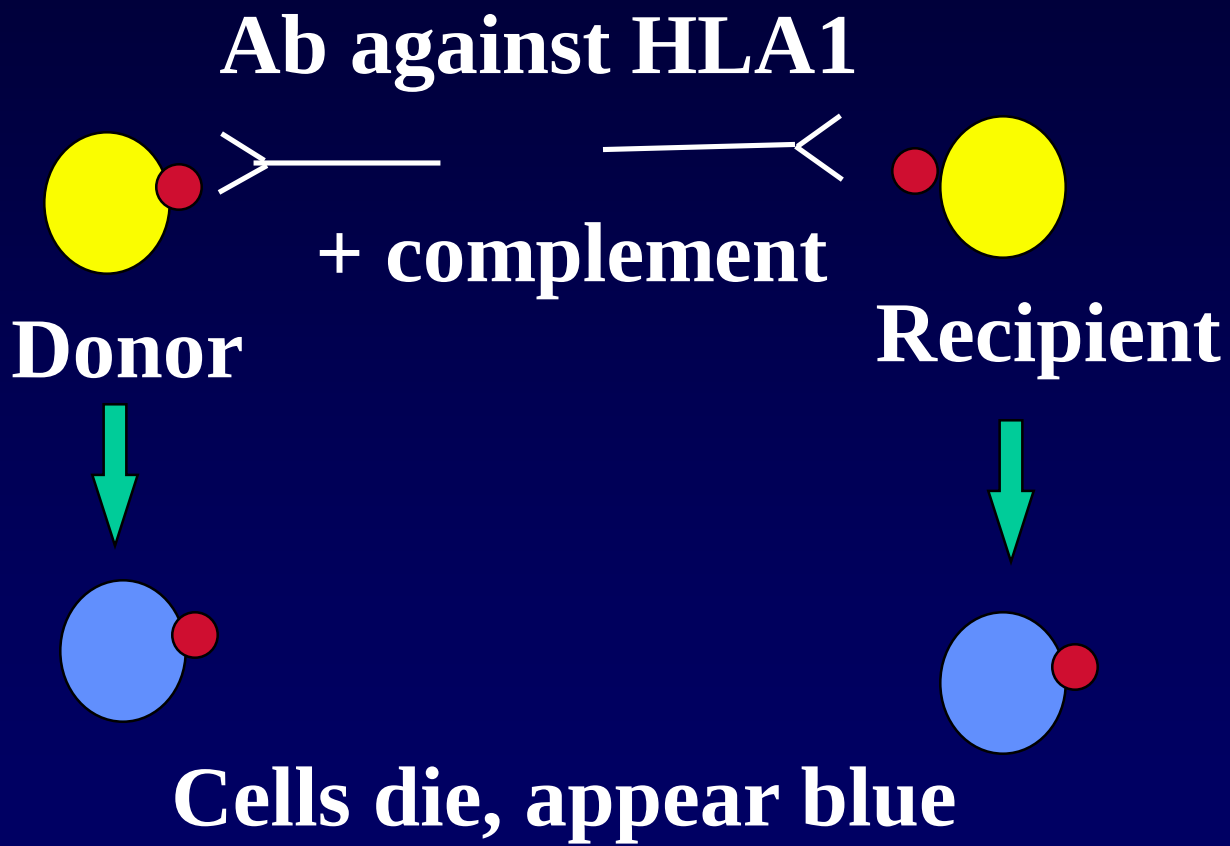
- Class I antigens: constitutively expressed on surface of most cells
- Class II antigens: expressed on cells of lymphoid system
- Expression of MHC molecules can be upregulated by ischemia, etc.
- nomenclature
  - HLA (human) class I: A, B, C; class II: DR, DQ
  - H-2 (mouse) class I: K, D, L; class II: IA, IE

Identifying MHC polymorphisms ('tissue typing')

- Formerly determined by antibodies against MHC molecules
  - **HLA typing**
  - **MLR**
- Now by DNA testing: allele-specific PCR, sequencing

Tissue Typing(or HLA-typing)

Used to identify HLA molecules on cells



Mixed Lymphocyte Reaction:

- Strong Proliferation--->High incompatibility
- Weak proliferation--->Low incompatibility
- No proliferation---> 100% compatibility
- Helps to identify any antigenic differences between donor and recipient

Types of transplant graft rejection

- Antibody-mediated rejection (AMR)
  - Hyperacute rejection
  - Acute or delayed AMR
- Cellular rejection
- ‘Chronic’ rejection

Does MHC (HLA) ‘matching’ prevent rejection?

- Reduces rejection but there are still ‘minor histocompatibility antigens’ (MiHA)
- MiHA are probably polymorphisms affecting peptides in the grooves
- But we cannot MHC-match most grafts: *too much polymorphism, too little time, too few donors*
- Therefore need immunosuppression

Matching and cross-matchingq

- Matching: finding a donor who shares the HLA antigens of the recipient, to minimize antigen disparities
  - requires donor and recipient antigens to be identified
- Cross-matching: testing the SERUM of the recipient for antibodies against the donor antigens

HLA-sensitization

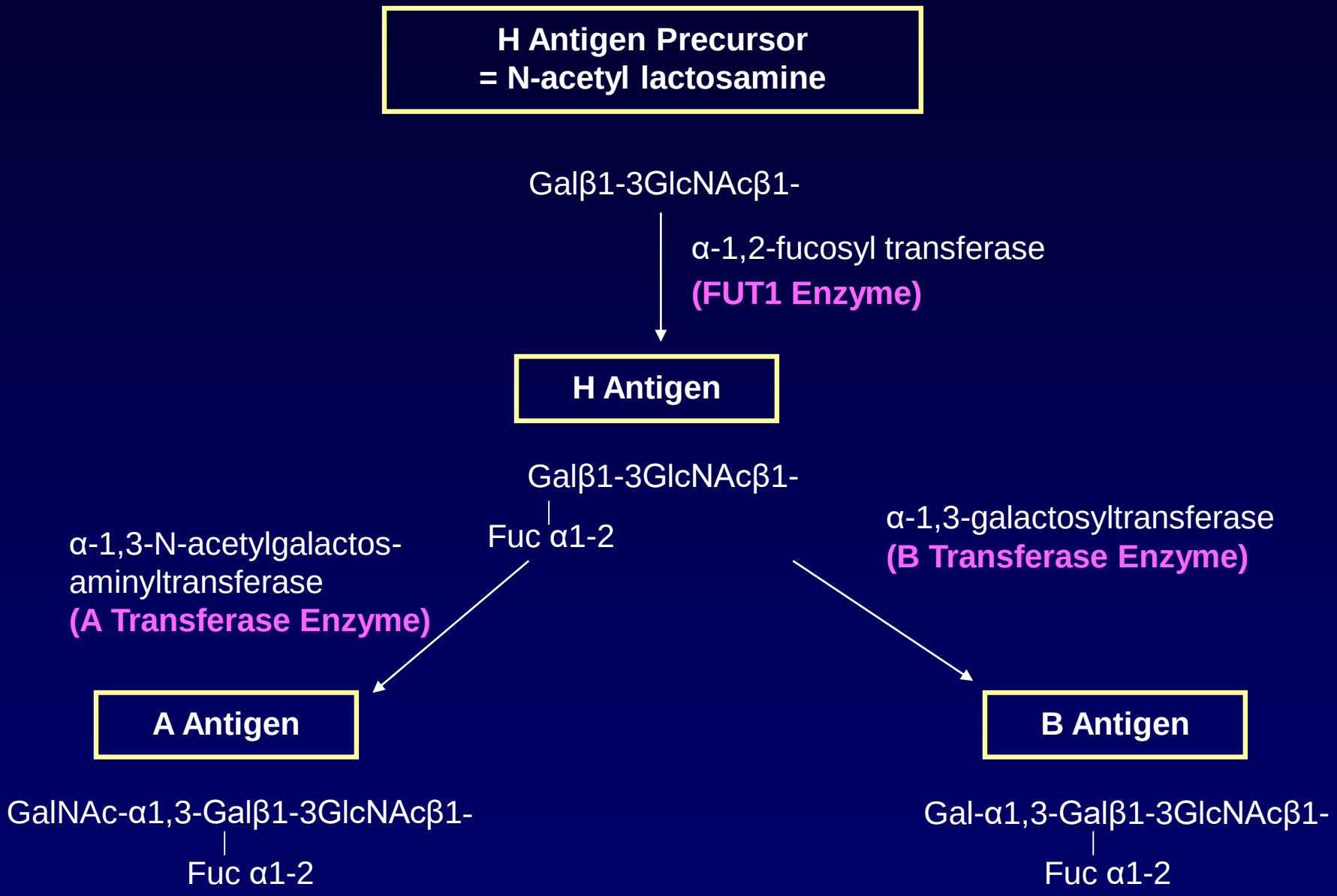
- Exposure to non-self HLA antigens can cause production of HLA-directed antibodies
- Common causes of HLA-sensitization include blood transfusions, pregnancies, previous transplants
- In infants, tissue patches implanted during cardiac surgery cause sensitization

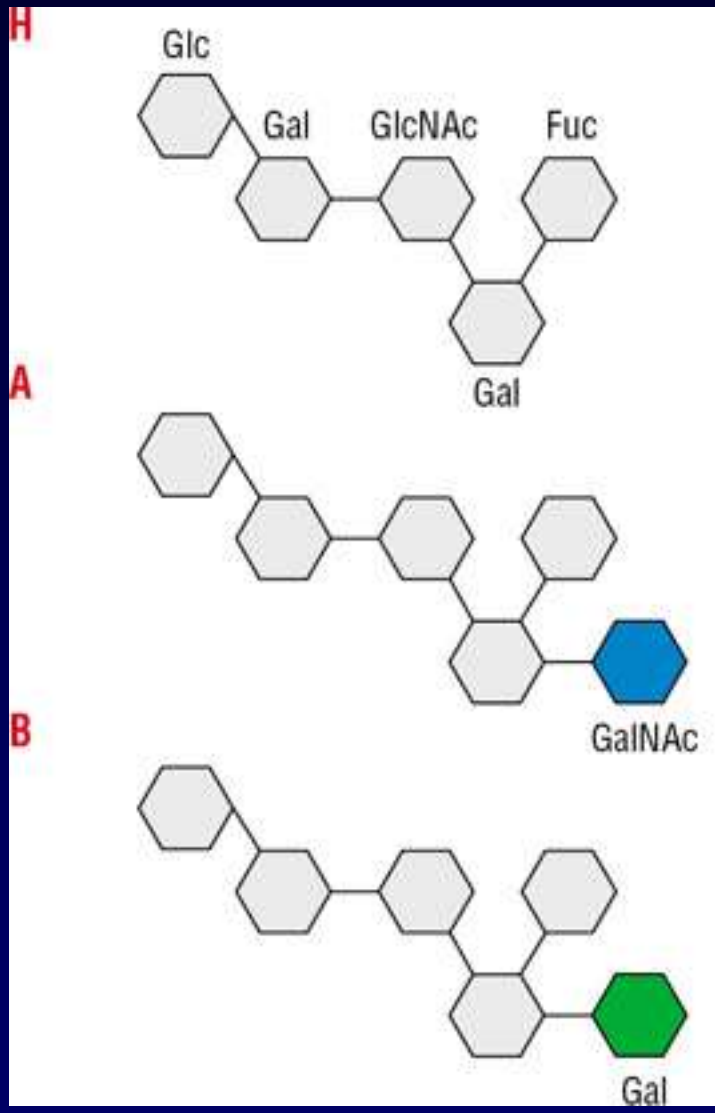
Transplantation antigens (2)

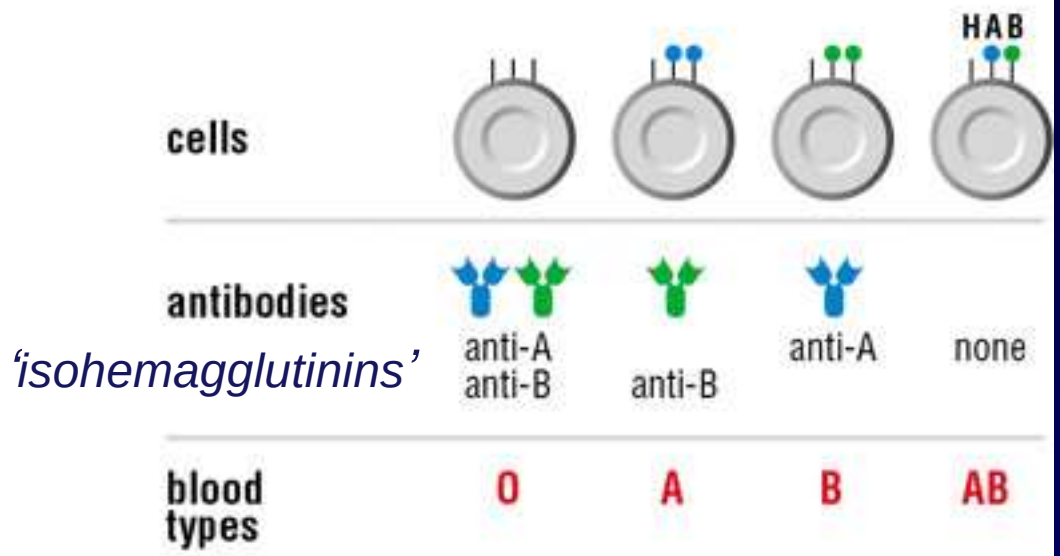
ABO system

- ABH antigens are complex carbohydrate (polysaccharide) structures on surface of many cell types including graft cells & RBC; genes encode production of specific glycosyltransferases catalyze addition of terminal trisaccharide
- nomenclature
  - H antigen: base chain; defines blood type O
  - A trisaccharide on H chain: blood type A or A1
  - B trisaccharide on H chain: blood type B
  - A and B trisaccharides on H chains: blood type AB

ABO Antigen Biosynthetic Pathway







'isohemagglutinins'

ABO compatibility between donor and recipient is crucial to avoid rapid graft rejection

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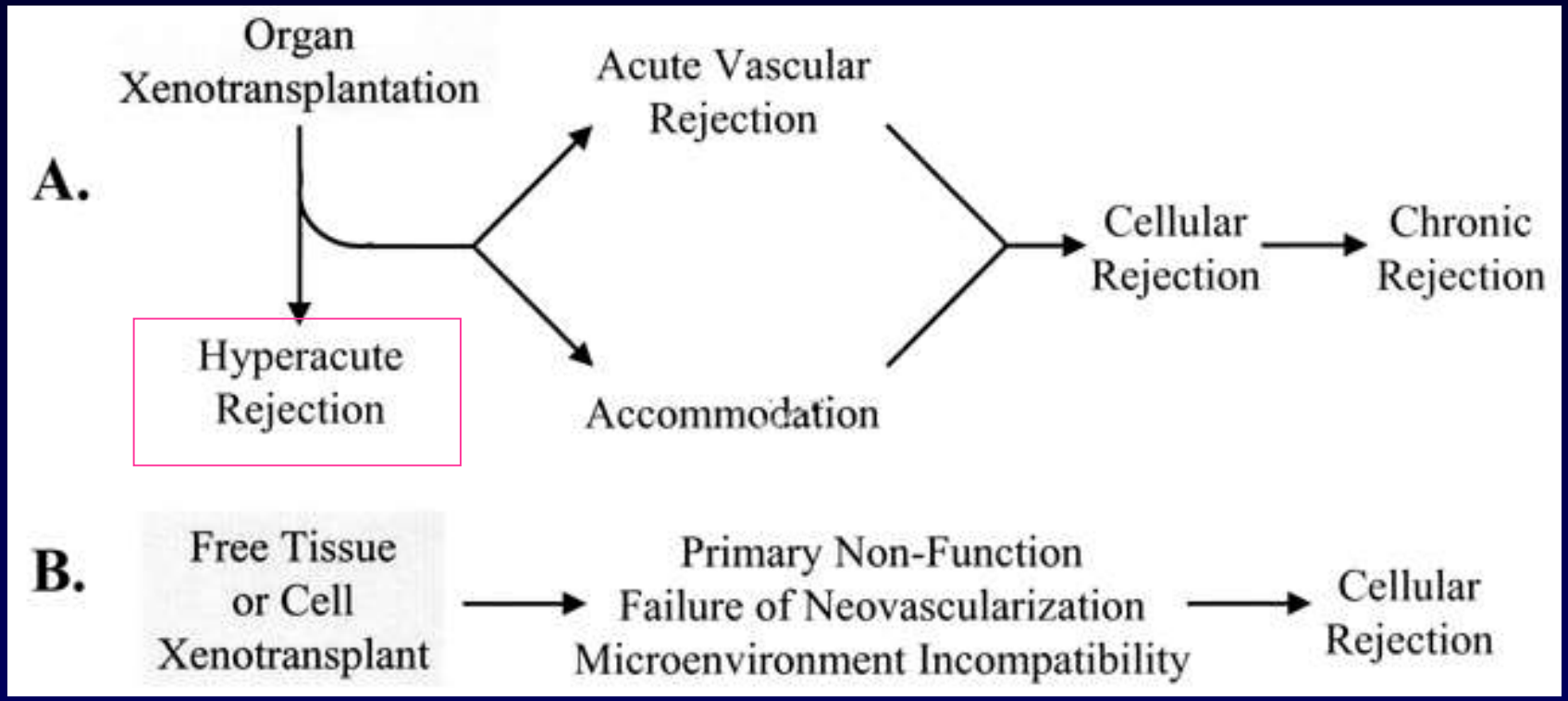
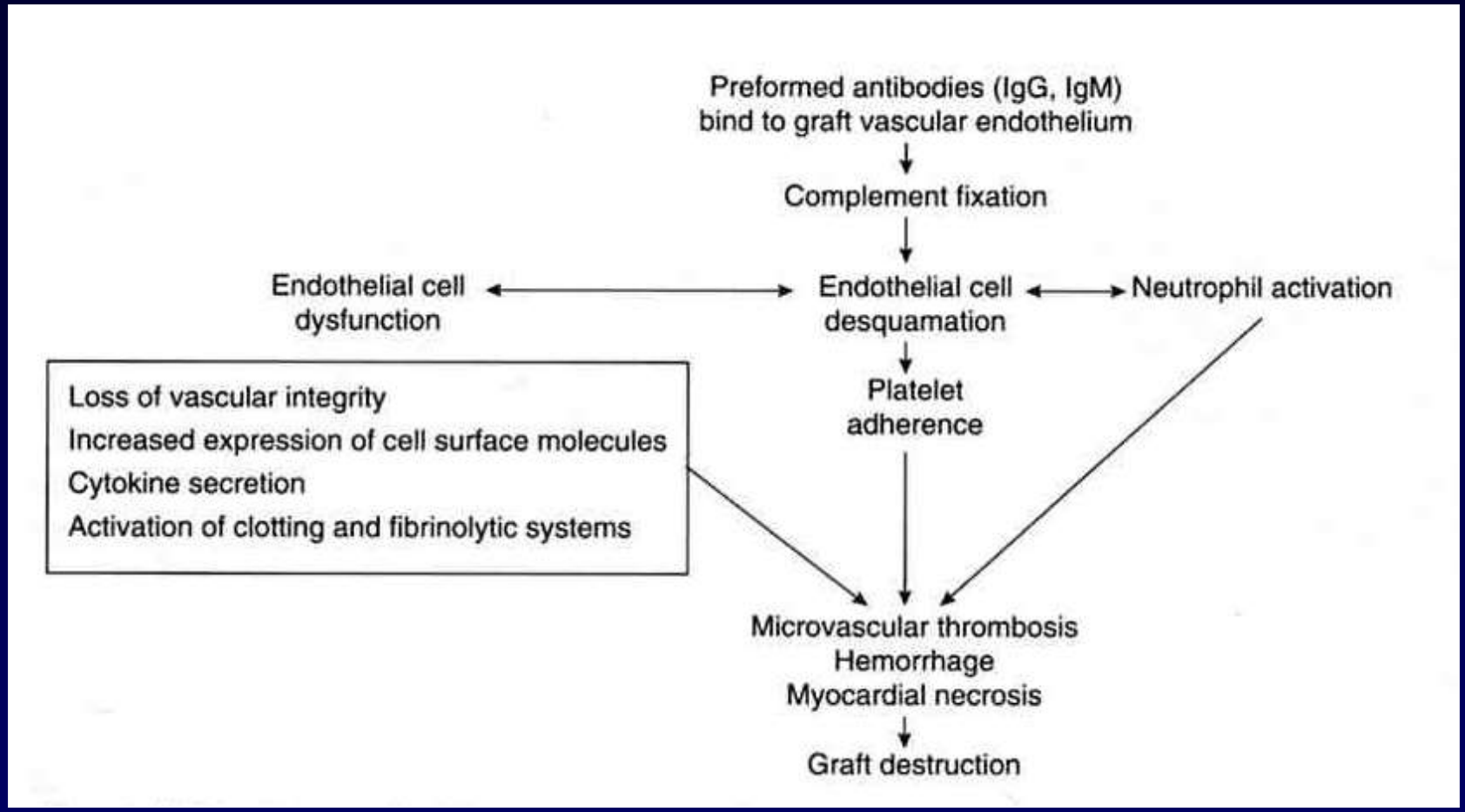
The ABO blood group barrier in organ transplantation

- ‘ABO’ antigens: carbohydrate structures expressed on many tissues and organs, including endothelium of organ transplants
- Recipient pre-formed ‘natural’ anti-A or anti-B antibodies to *non-self* A/B antigens

- Transplantation of ABO-incompatible organs:

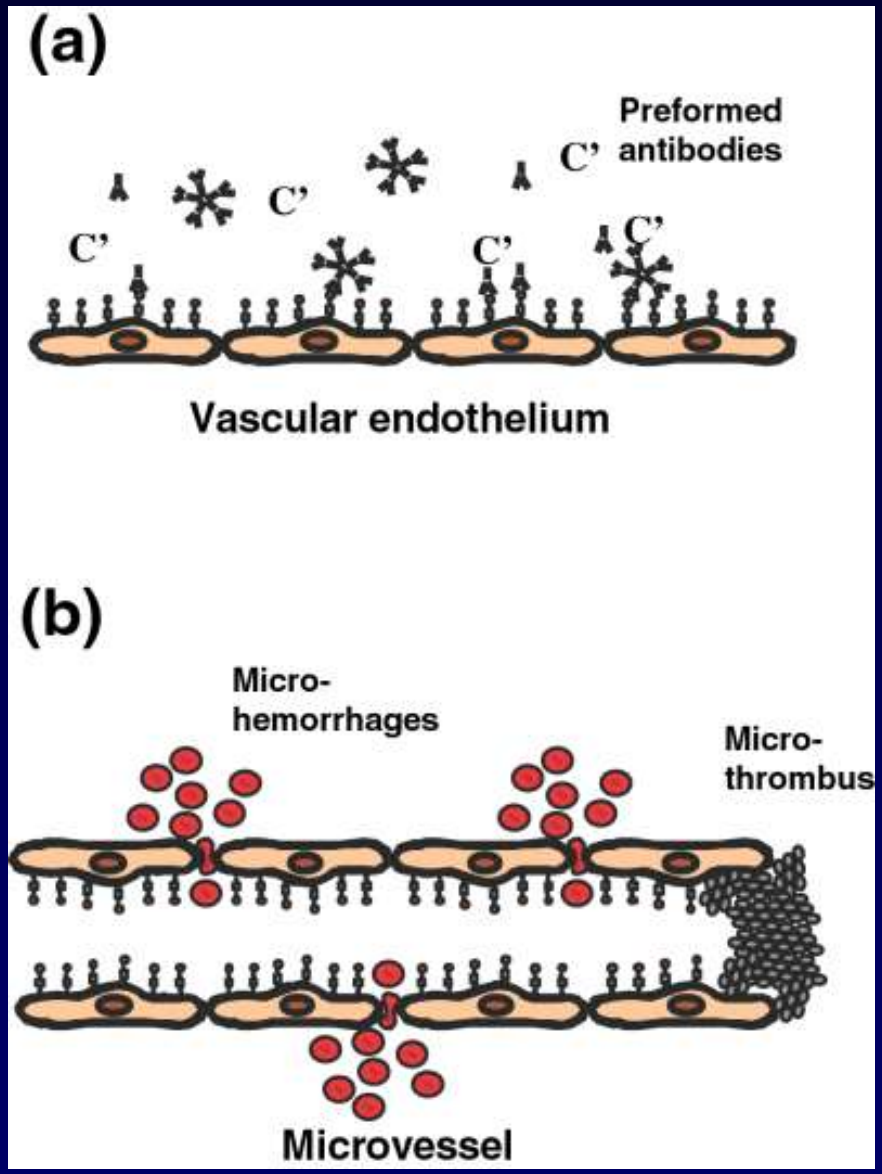
→ ***‘Hyperacute’ rejection***


A.
Organ Xenotransplantation
Hyperacute Rejection
Acute Vascular Rejection
Accommodation
Cellular Rejection
Chronic Rejection
B.
Free Tissue or Cell Xenotransplant
Primary Non-Function
Failure of Neovascularization
Microenvironment Incompatibility
Cellular Rejection



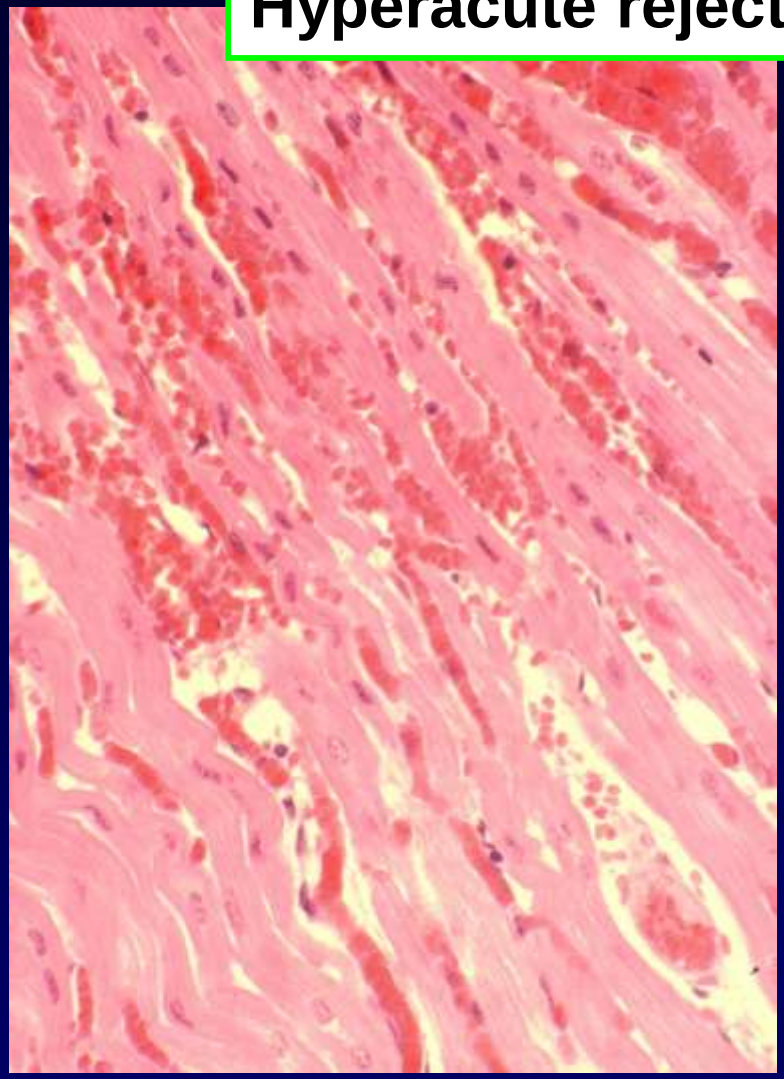
Pathogenesis of hyperacute rejection

From Silver *et al*.

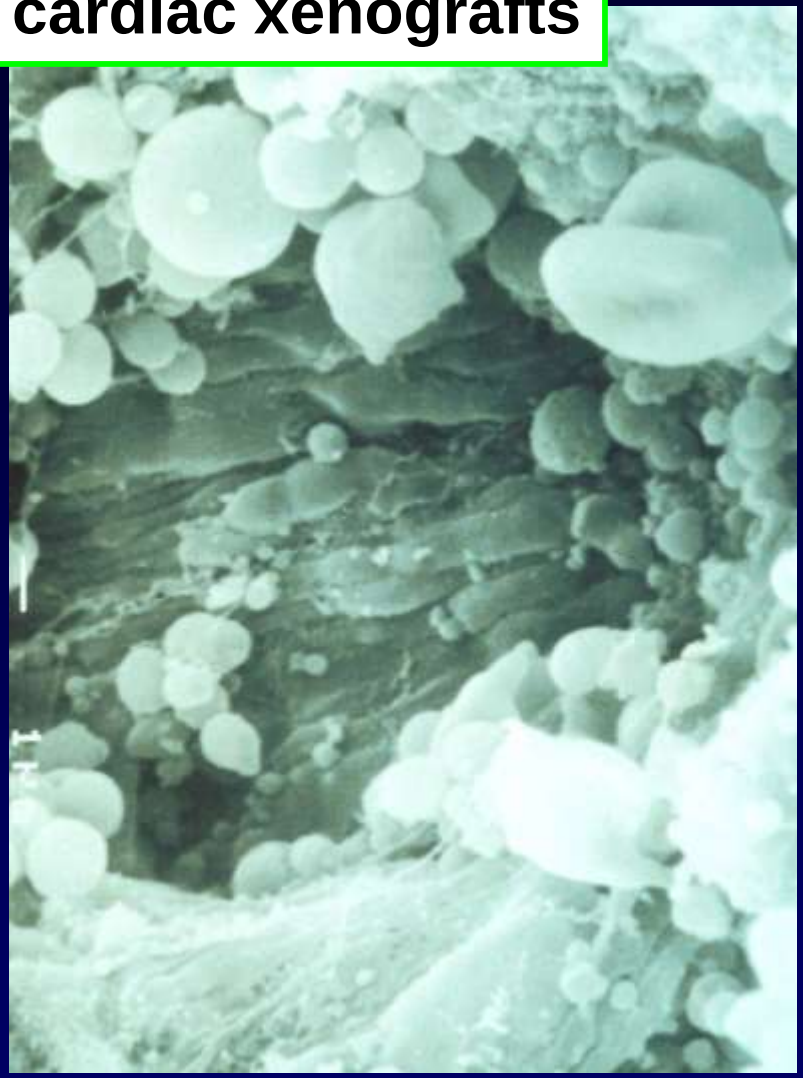

(a)
Preformed antibodies
C'
C'
C'
C'
C'
Vascular endothelium
(b)
Micro-hemorrhages
Micro-thrombus
Microvessel

"BOY! TALK ABOUT ORGAN REJECTION!"

Hyperacute rejection of cardiac xenografts

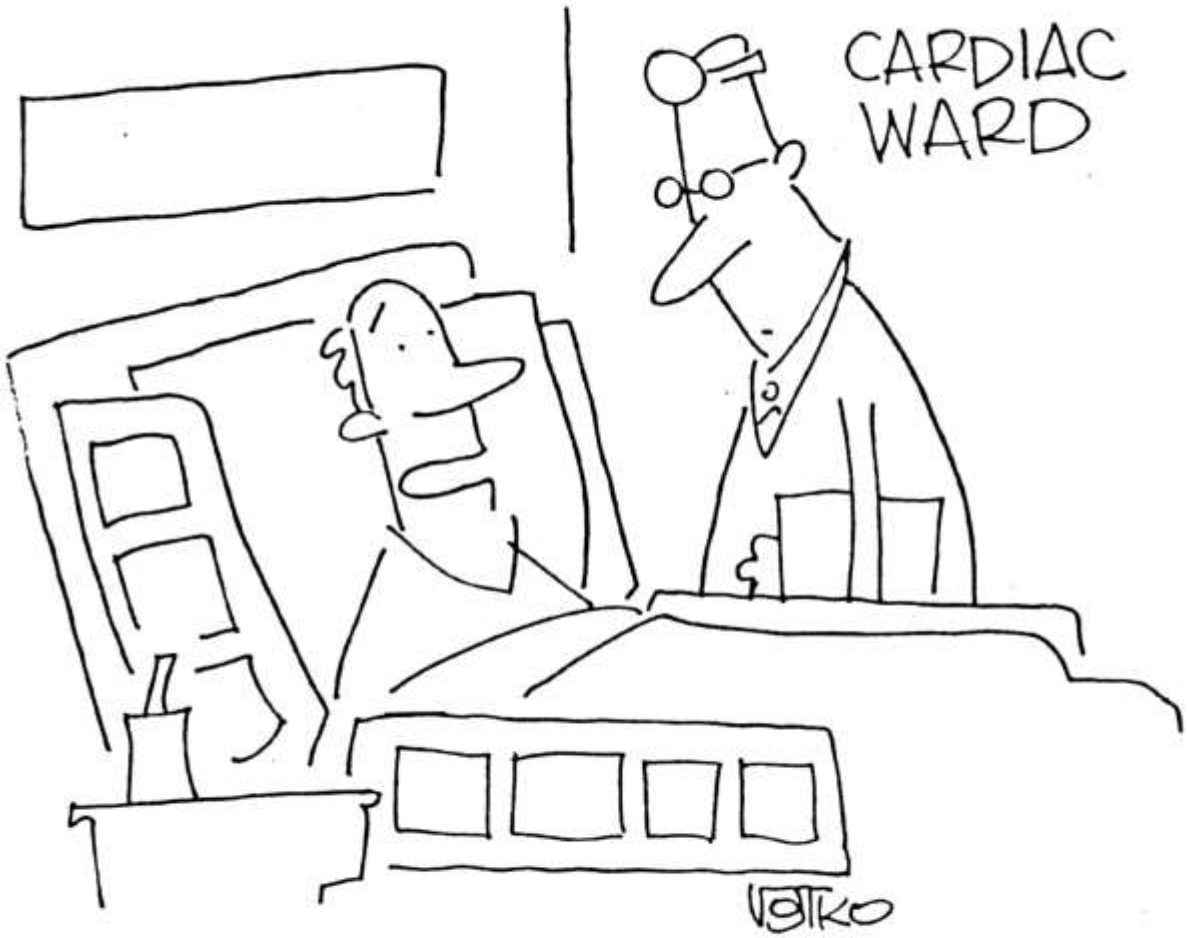


Pig to baboon; 30 min.



Guinea pig to rat; 5 min.

Courtesy of Dr. Jeff Platt, Transplantation Biology, Mayo Clinic



"I'm a vegetarian. Any chance of getting an artichoke heart?"

Humoral immunity in human infants

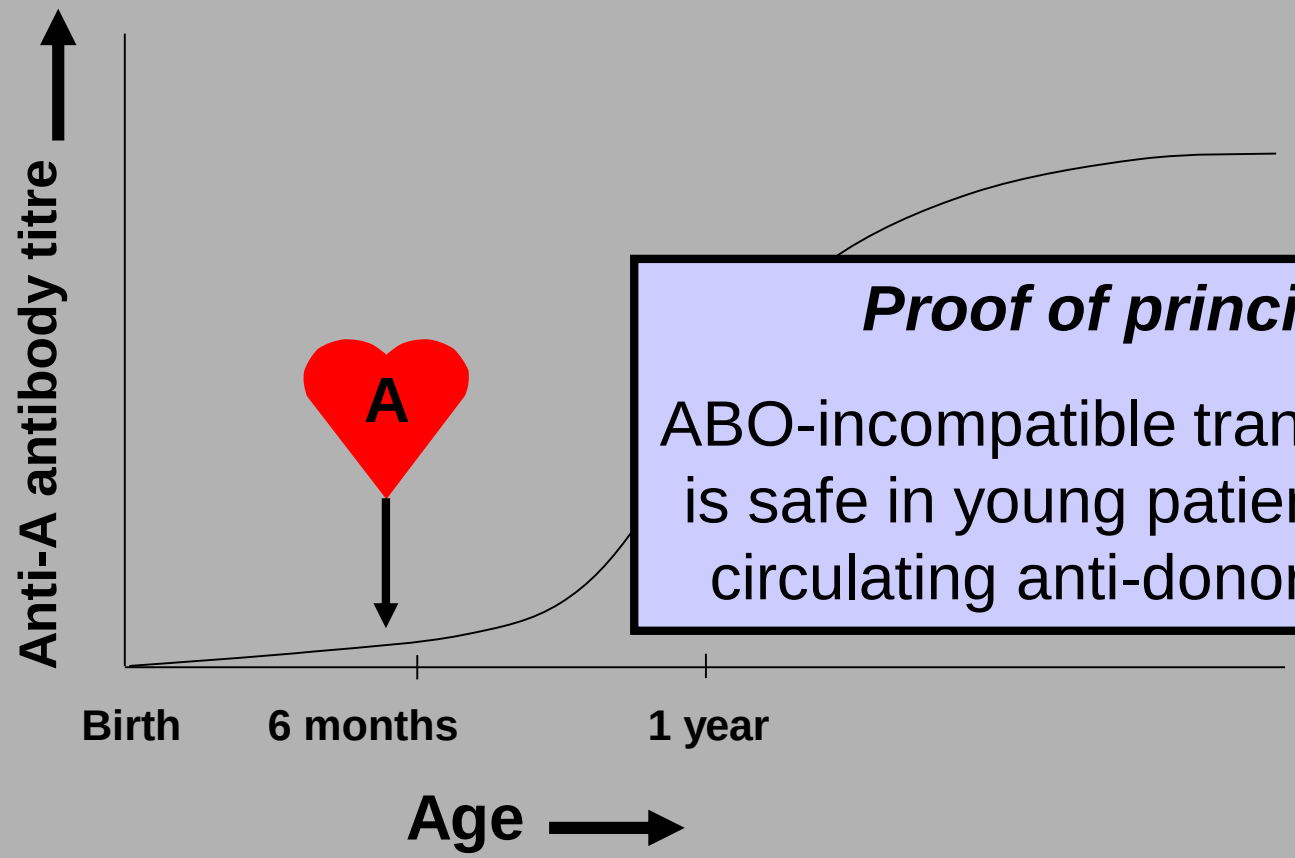
To **protein** antigen stimulation (T cell ‘dependent’):

- generally competent antibody response
- (generally competent cell-mediated responses)

To **carbohydrate** antigens (T cell ‘independent’):

- generally impaired antibody responses

Isohemagglutinin ontogeny in normal human infants



Proof of principle:

ABO-incompatible transplantation is safe in young patients without circulating anti-donor antibody

West et al., NEJM 2001; 344

Types of transplant graft rejection

- Antibody-mediated rejection (AMR)
  - Hyperacute rejection
  - Acute or delayed AMR
- Cellular rejection
- ‘Chronic’ rejection

Rejection mechanisms

- Anti-HLA alloantibody (plus C/leukocytes)
  - target of endothelium of interstitial capillaries
  - late capillary basement membrane multilayering
  - late glomerular deterioration
- T cell-mediated rejection
  - lymphocyte infiltration into graft
  - cytotoxic destruction of graft parenchymal cells
  - key role also for macrophages and *non-cytotoxic* destruction (DTH)
  - target is endothelium and epithelium (and intima of small arteries)
  - intimal arteritis (uncommon): neointima and disruption of elastic lamina; inflammatory cells

Allograft rejection

Kidney response to injury

antigen presenting cells move to lymphoid organs

APCs trigger T cells in secondary lymphoid organs

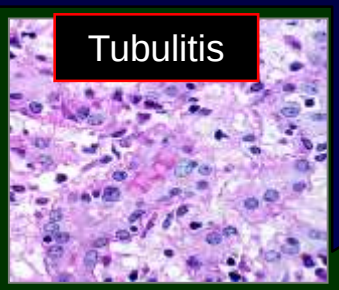
central memory T cells recirculate between secondary lymphoid organs

Host-graft adaptation

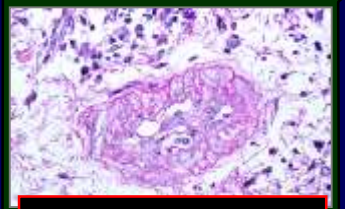
Effector T cells home to inflamed sites: CD8, CD4

e.g. CCR7

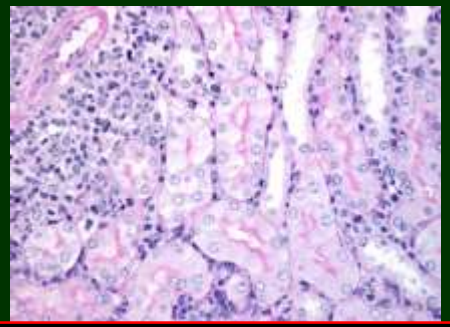
Helper T cells help B to make alloantibody



Tubulitis



Intimal arteritis

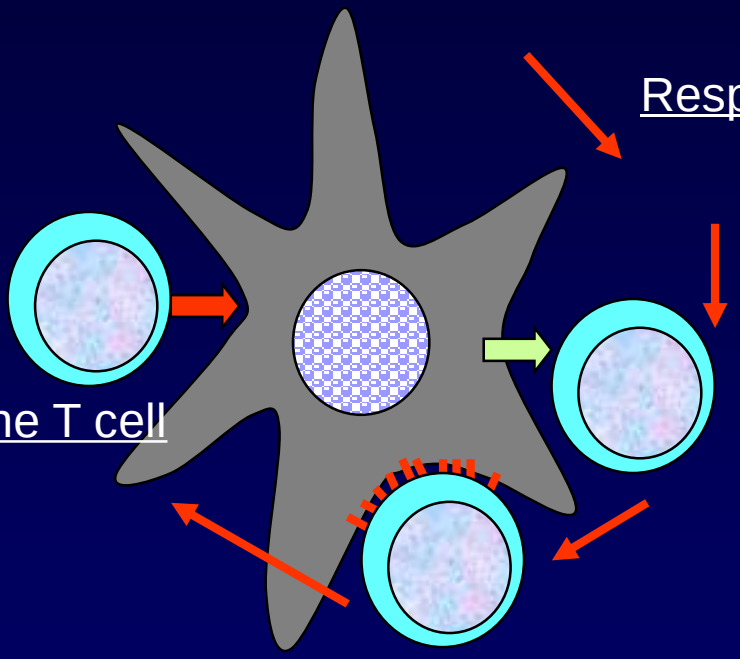


Interstitial
CTL-macrophage infiltrate

Discrete molecular processes in T cell-mediated rejection

- CTL infiltration
- IFN-γ production and effects on graft
- IFN-γ suppression of some gene patterns
- Macrophage (and DC) entry/activation
- Injury and repair
  - mild to moderate (can be restored)
  - severe (likely will lose graft cells)
  - fibrosis is part of both
  - parenchymal de-differentiation
- B cells/plasma cell infiltration

Dendritic cells engage T cells

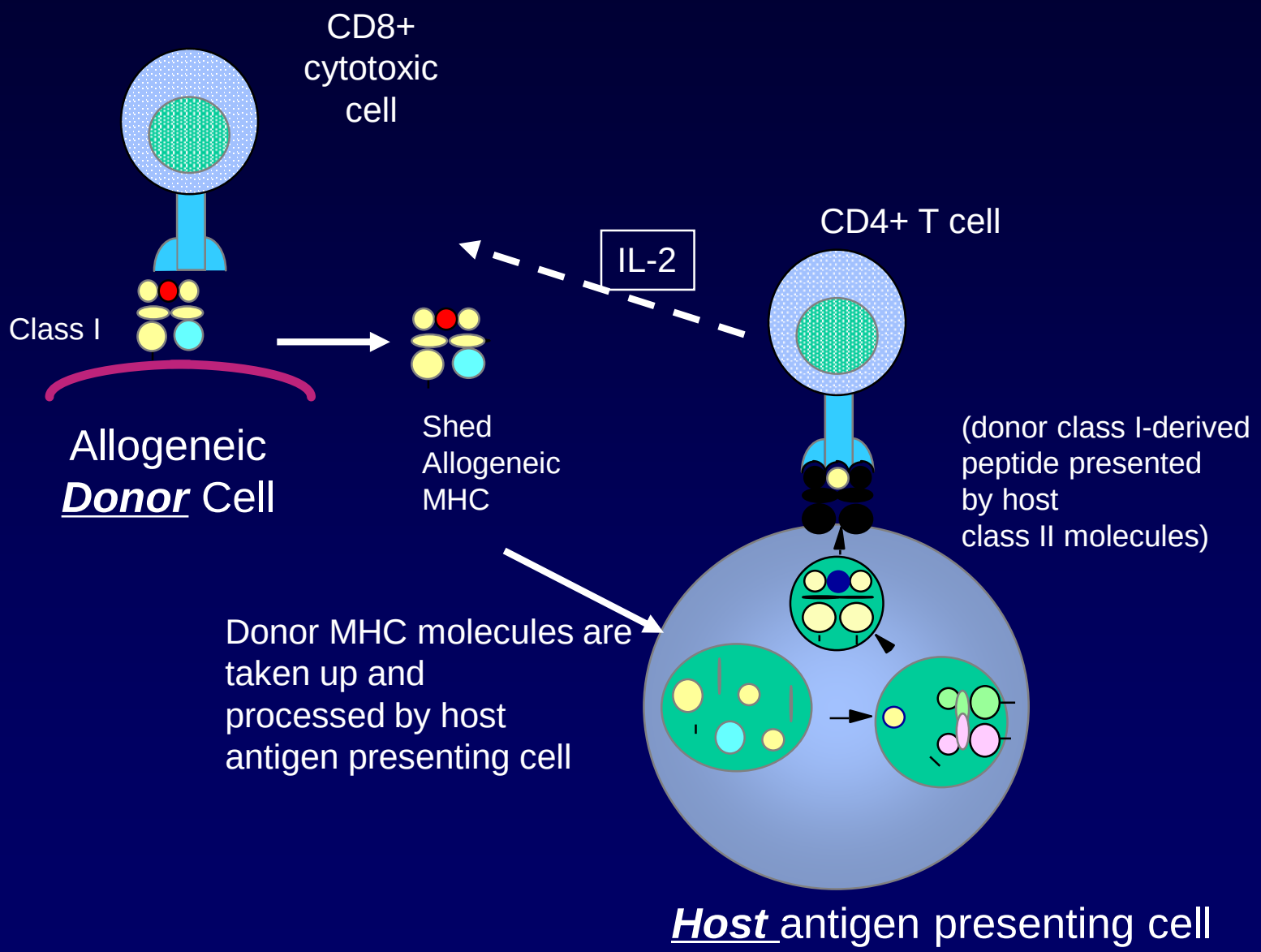


The Immunologic Synapse
CD58,CD86,MHC-peptide

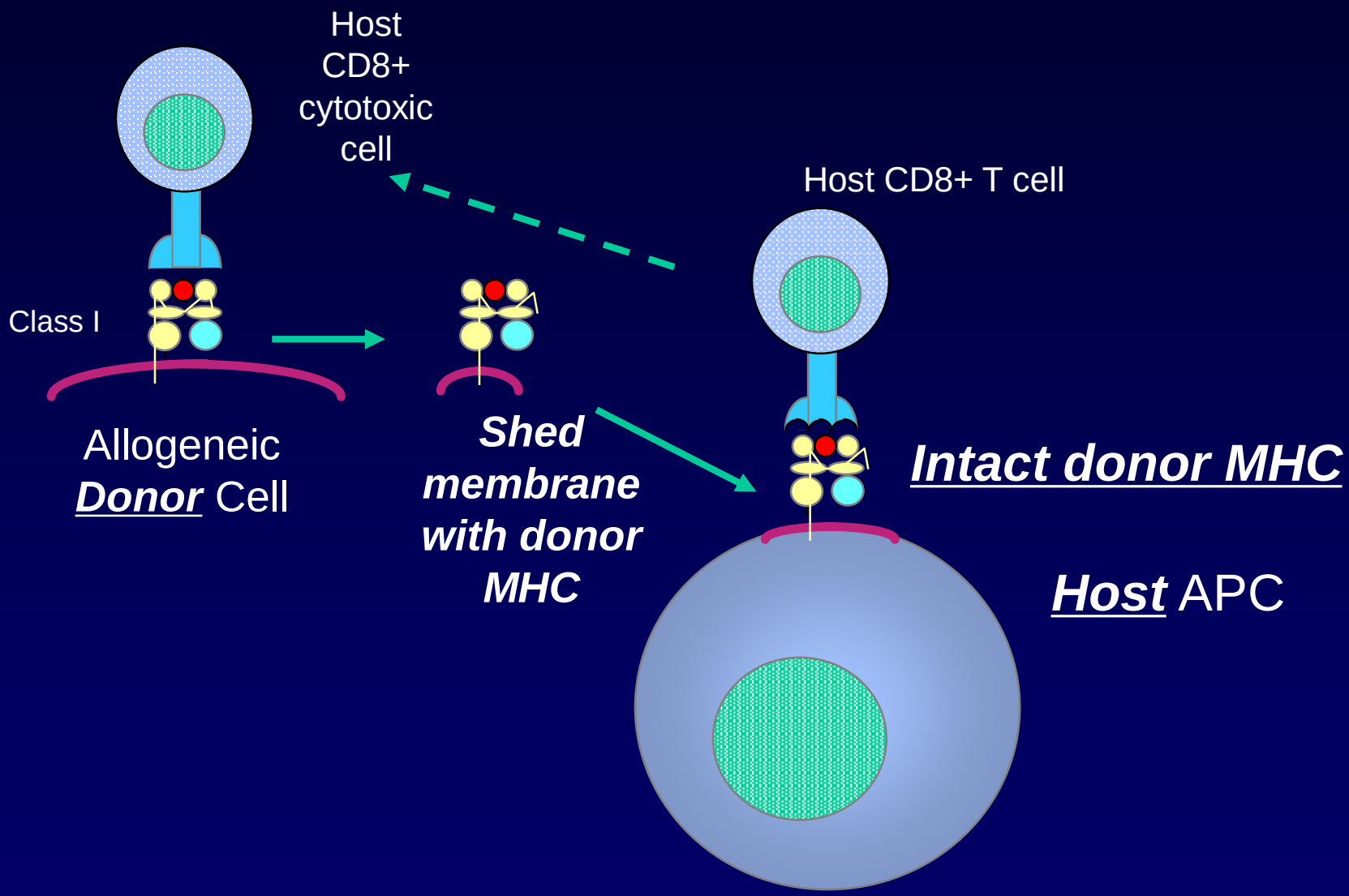
Antigen presentation

- Direct: donor APCs with intact donor MHC
- Indirect: host APCs present peptides from donor MHC
- Semi-direct: host APCs present intact donor antigen taken up as a membrane patch

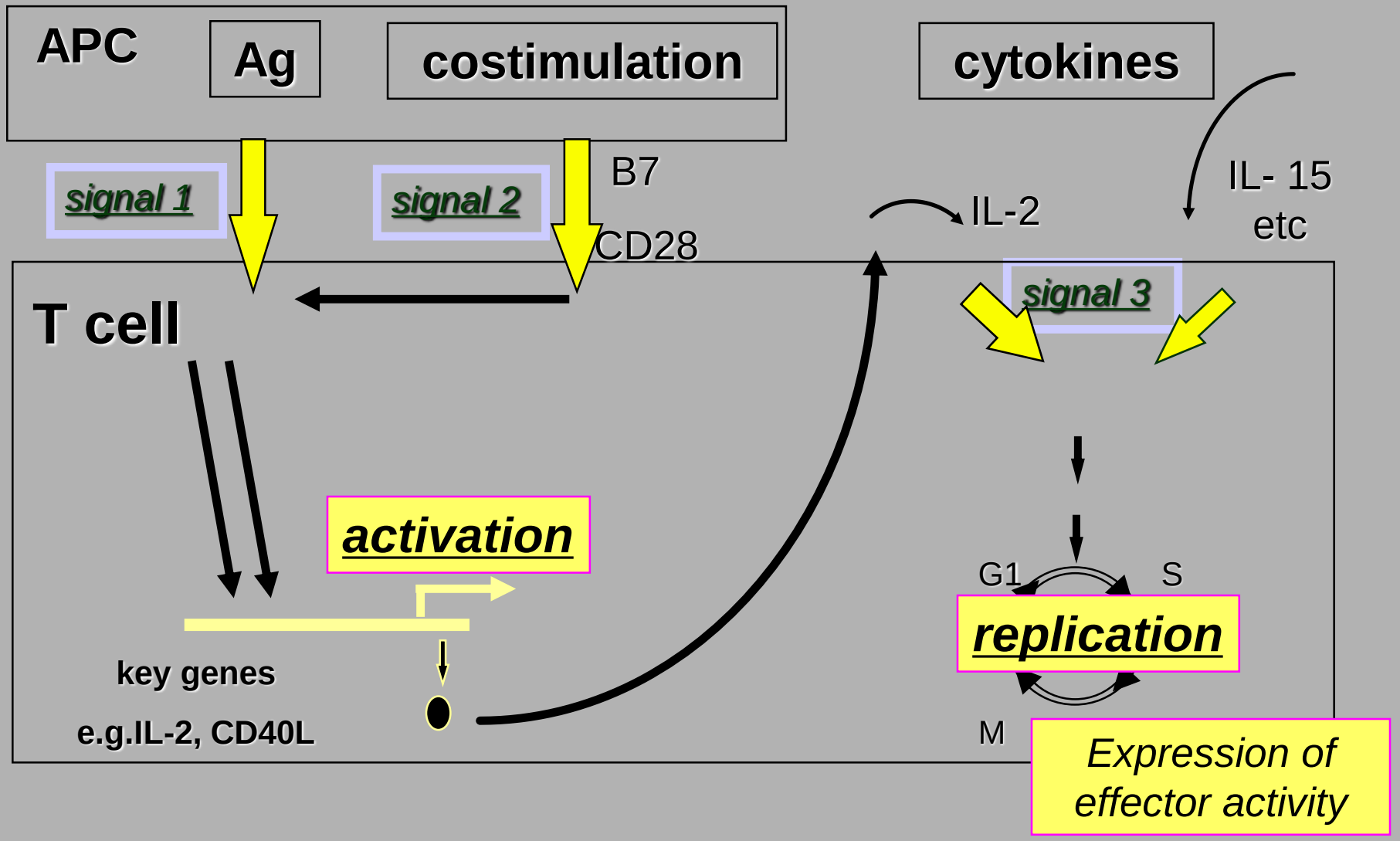
Allorecognition: indirect pathways



Semi-direct antigen presentation the membrane patch pathway



3 signals for T cell responses



Types of transplant graft rejection

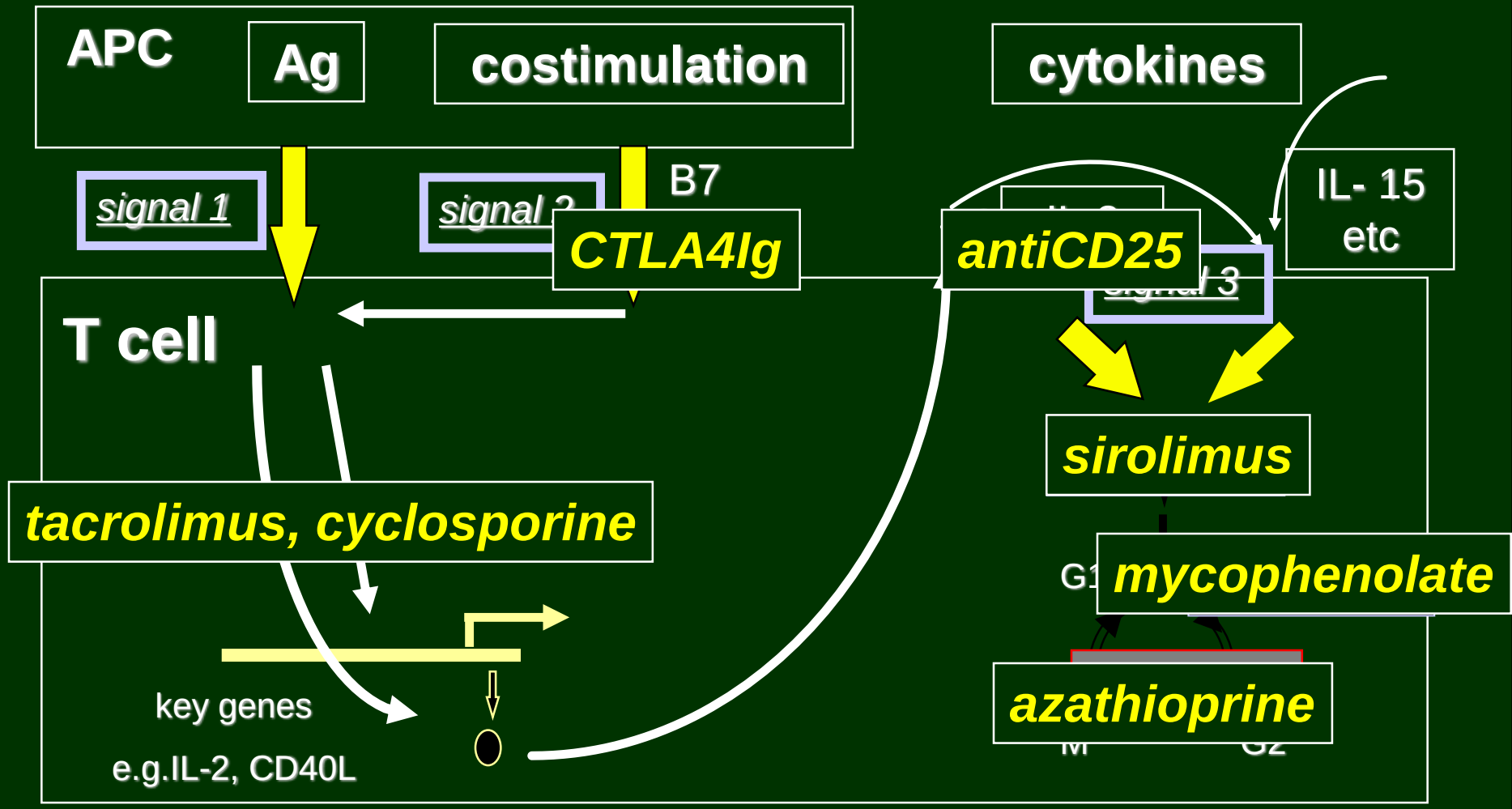
‘Chronic rejection’:

- Poorly defined term indicating chronic deterioration within graft
- Occurs in some form in all organ allografts
  - Kidney: chronic allograft nephropathy
  - Heart: graft coronary artery disease
  - Lung: bronchiolitis obliterans syndrome
  - Liver: vanishing bile duct syndrome
- May (or may not) be associated with recurrent cellular rejection episodes
- Alloantibody may (or may not) play a role
- Not prevented with current immunosuppressive drug therapies

Immunosuppressive drugs

- Glucocorticosteroids: prednisone
- Small molecule drugs
  - azathioprine
  - calcineurin inhibitors: cyclosporine, tacrolimus
  - target of rapamycin inhibitors: sirolimus (a.k.a rapamycin)
  - IMPDH inhibitors: mycophenolate mofetil
  - lymphocyte recirculation (S-1-P) inhibitors: FTY720
- Depleting antibodies
  - rabbit polyclonal antilymphocyte globulin
  - anti CD52 (Campath-1h), anti CD3
  - B cell depletion: anti CD20
- Non-depleting antibodies and fusion proteins
  - anti CD25
  - CTLA4Ig fusion protein

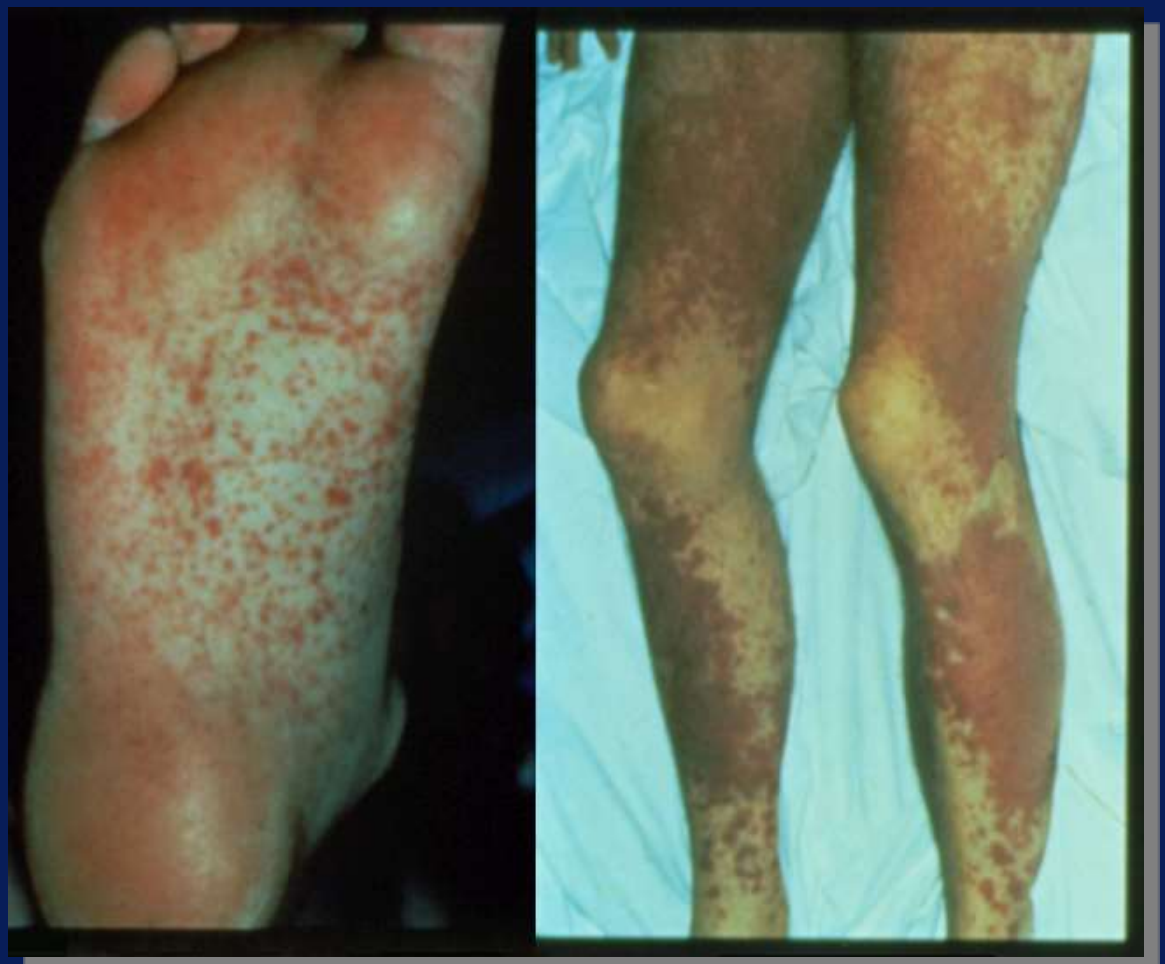
Where immunosuppressive drugs act



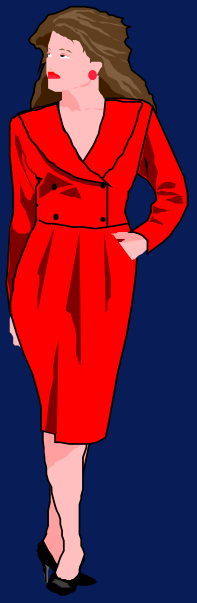
Graft versus Host Reaction (GVHR)

- When grafted tissue has mature T cells, they will attack host tissue leading to GVHR.
- Major problem for bone marrow transplant.
- Methods to overcome GVHR:
  - Treat bone marrow to deplete T cells.
  - Use autologous bone marrow.
  - Use umbilical cord blood.

GVH disease in humans



Why is fetus not rejected by the mother?

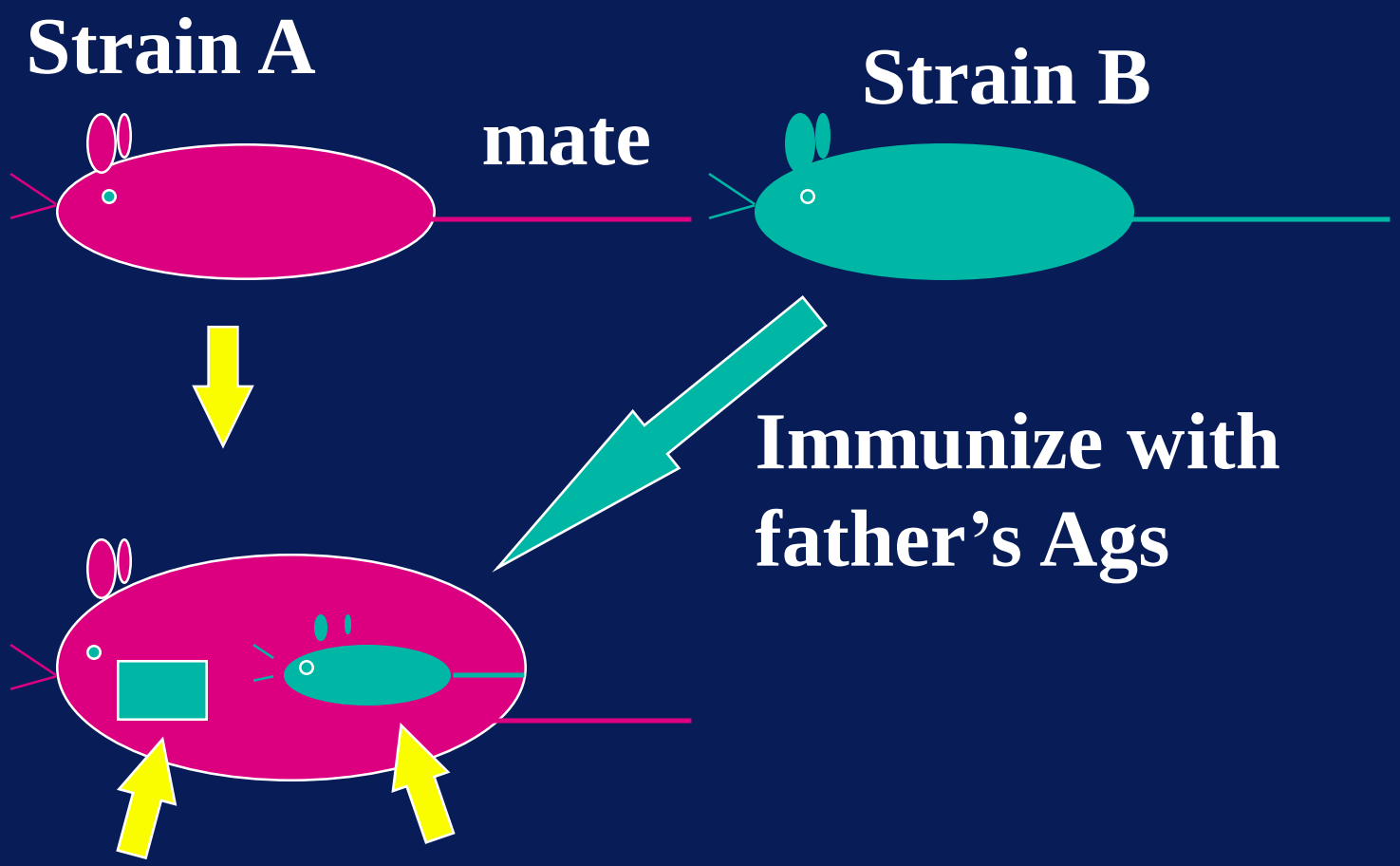


A/B

C/D

A/C, A/D, B/C, B/D

Fetus as an allograft



Why is fetus not rejected?

- Placenta acts as a barrier or filter.
- It filters anti-MHC Abs.
- Trophoblast---outermost layer of fetal tissue---is in direct contact with maternal blood.
- Trophoblast expresses weak or no MHC.

Why is fetus not rejected?

- progesterone---hormone---immunosuppressive.
- Placenta expresses FasL.
- Spontaneous abortions are some times triggered by maternal immune response against fetus.

Ethical aspects

Organs for sale !

Ethical aspects:

- Thanks to Allah ---MHC is polymorphic.

Summary

- Why allografts are rejected?
- How to match donor and recipient?
  - HLA typing
  - MLR
- Who is the best organ donor?
- What drugs are used to prevent graft rejection?
- Why does mother not reject fetus?

The End