Transplantation

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Objectives

- To understand the diversity among human leukocyte antigens (HLA) or major histo-compatibility complex (MHC)
- To know the role of HLA antigens in transplant rejection
- To be familiar with types of immune responses mediating transplant rejections and importance of tissue matching
- To understand the principles of management after transplantation

Major Histocompatibility Complex and Transplantation

- Major histocompatibility complex (MHC) proteins were discovered for the first time with the advent of tissue transplantation
- The success of tissue and organ transplantation depends upon the donor's and recipient's "***human leukocyte antigens***" (HLA) encoded by HLA genes
- These proteins are allo-antigens

MHC Class I and II Proteins

- MHC Class I are glycoproteins found on surface of virtually all the nucleated cells
  - Cytotoxic T cell kills virus infected cells in association with class I MHC proteins

- MHC Class II glycoproteins are normally found on the surface of antigen presenting cells (marophages, B cells, dendritic cells and Langerhans cells)
  - Helper T cell recognize antigen in association with class II MHC proteins

Major Histocompatibility Complex and Transplantation

- Genes for HLA proteins are clustered in the MHC complex located on the short arm of chromosome 6
- Three genes HLA-A, HLA-B and HLA-C code for Class I MHC proteins
- HLA-D loci encode for Class II MHC proteins ie, DP, DQ and DR

Major Histocompatibility Complex and Transplantation

Each individual has two "***haplotypes***" i.e, two sets of these genes one paternal and one maternal

MHC class	I			II			III	
Region	A	B	C	DP	DQ	DR	C4, C2, BF	
Gene products	HLA-A	HLA-B	HLA-C	DP	DQ	DR	C' proteins	TNF-α TNF-β
Polymorphisms	47	88	29	More than 300 HLA-D				

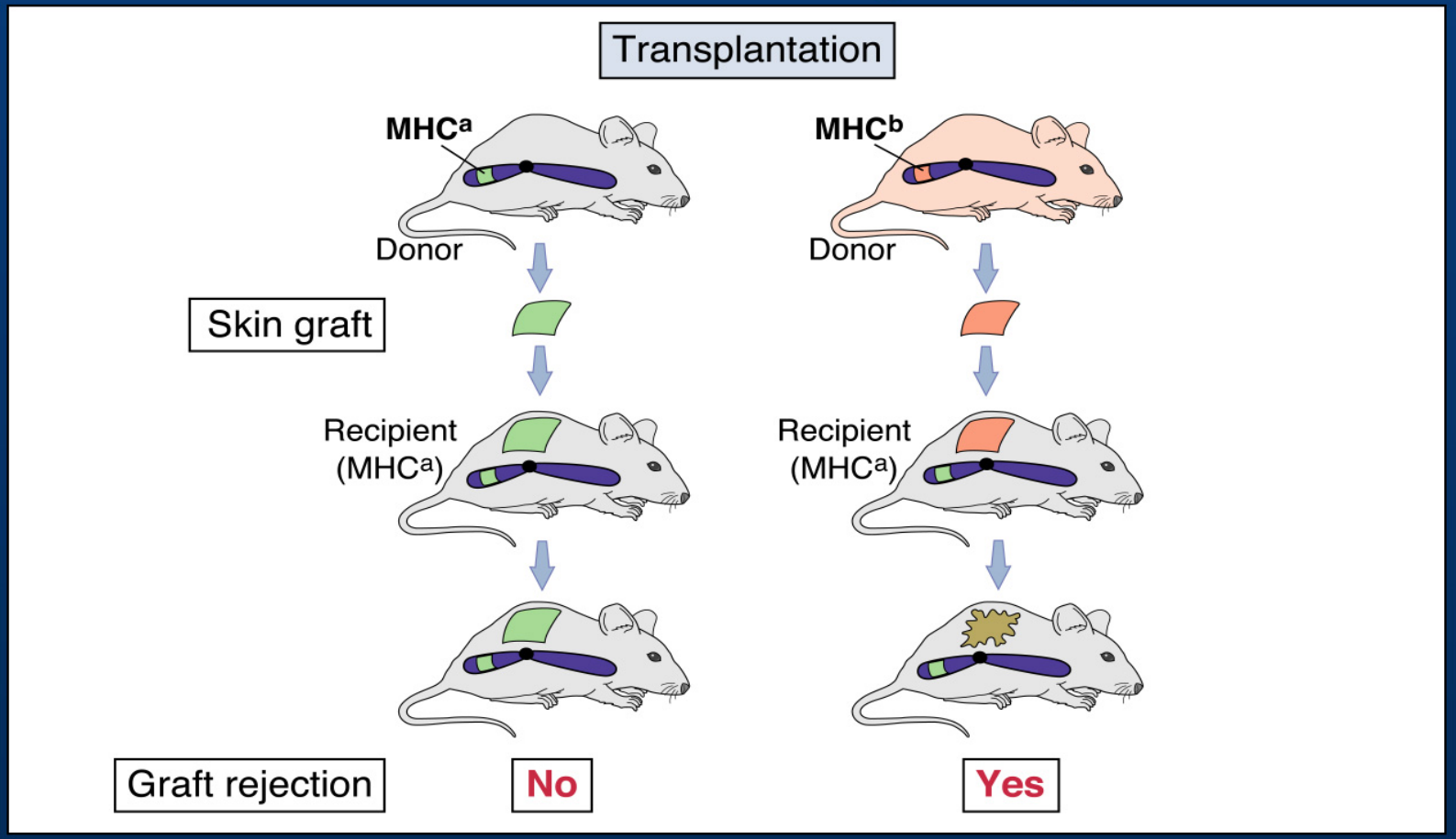
Minor HLA genes and Transplantation

- Minor HLA genes – unknown
  - They mount a weak immune response
  - Play role in chronic rejection of a graft
  - There are no laboratory tests to detect minor antigens

Transplantation antigens

Slide 4-2

MHC alleles control allograft rejection



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 4-2a

Transplantation

- Types of transplants:
  - Autografts, Autologous grafts
    - Donor and recipient are same individual
    - Common in skin grafting; bone marrow
  - Syngeneic grafts or (isograft)
    - Donor and recipient are genetically identical
    - Animal models; identical twins

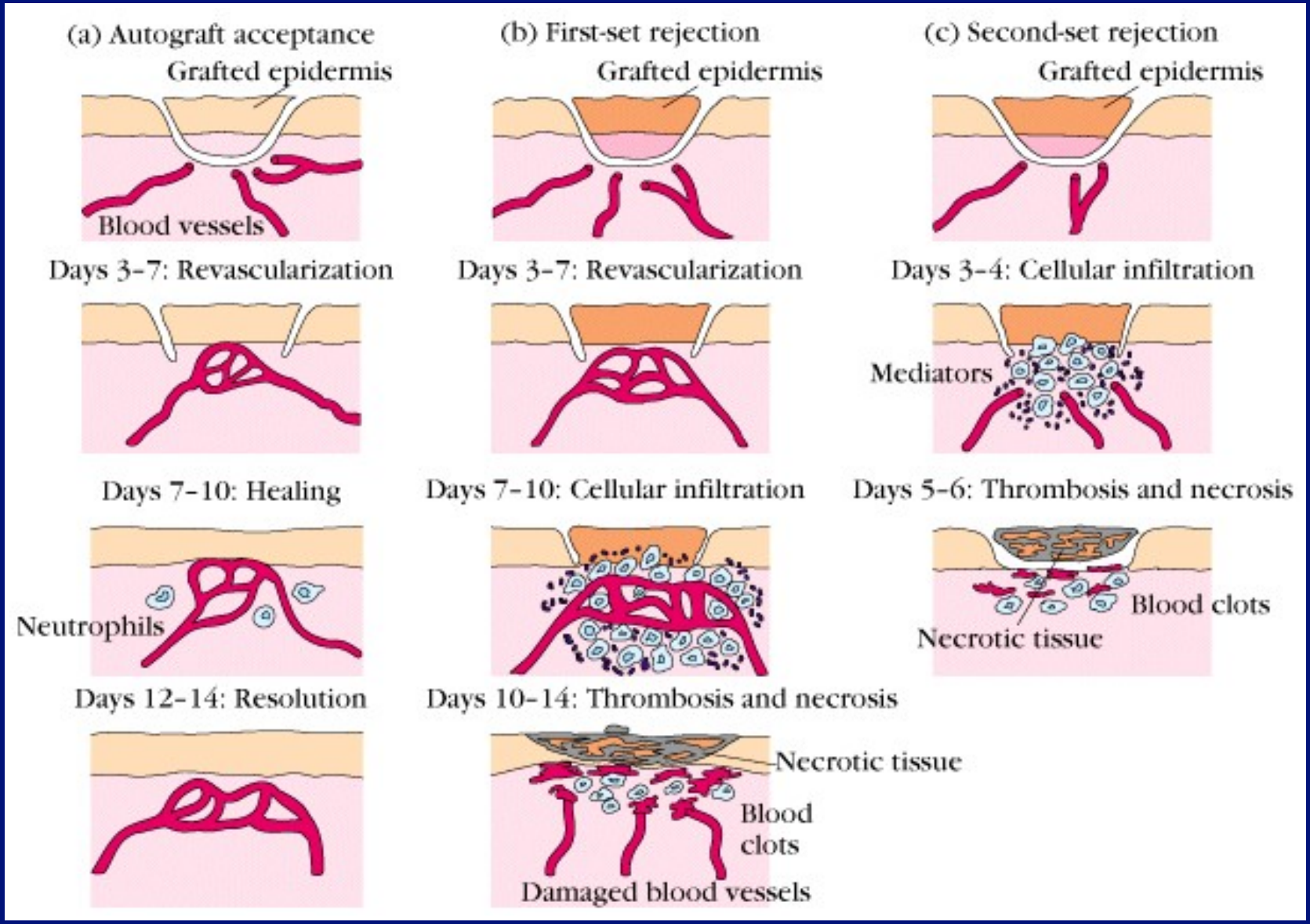
Transplantation

- Types of transplants:
  - Allogeneic grafts
    - Donor and recipient are same species, but genetically unrelated
    - Common heart, lung, kidney, liver graft
  - Xenogeneic grafts
    - Donor and recipient are different species
  - Artificial grafts

Transplantation (Rejection)

- Major Barrier to transplantation is the immune response
  - T cells play primary role
  - B cells can/do play a role
  - Classic adaptive/acquired immune response
    - Memory
    - Specificity

1st set versus 2nd set reactions

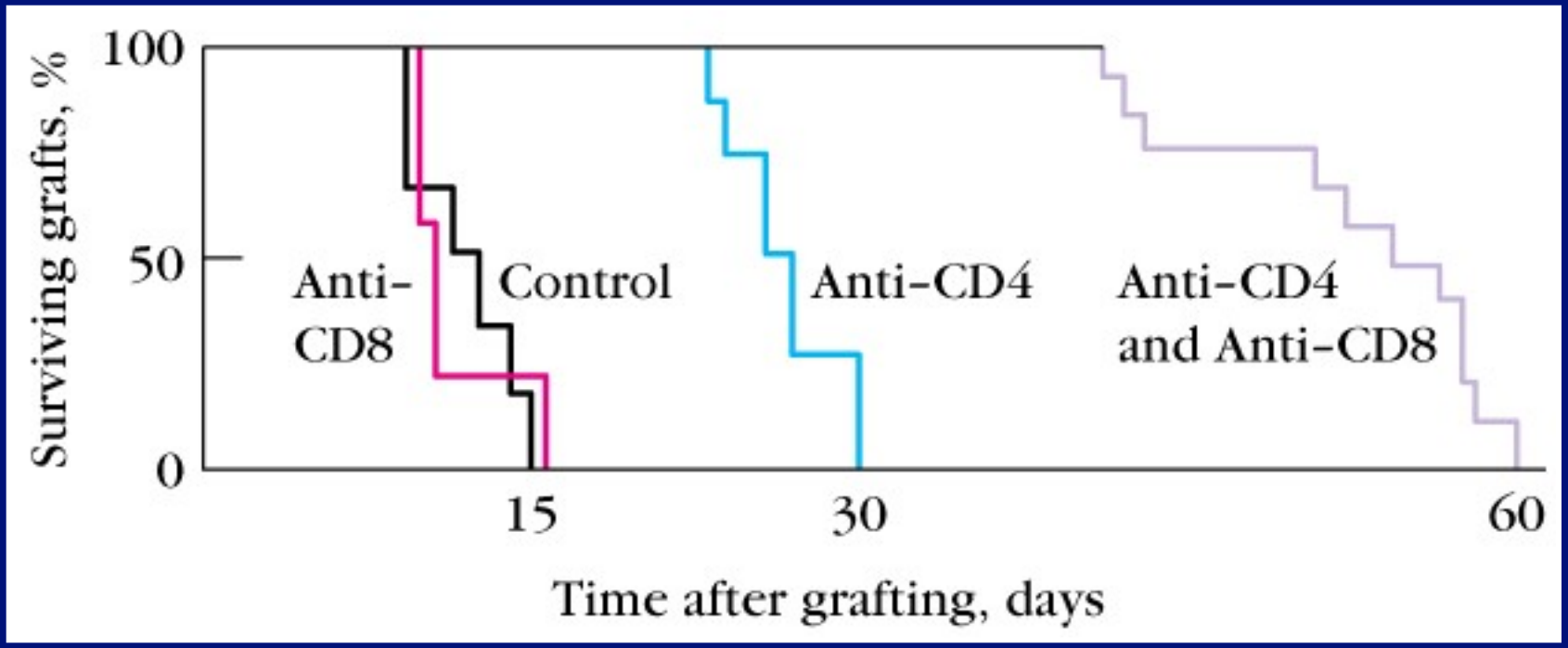


Transplantation

- T cells play primary role in 1st and 2nd set rejection reactions
  - Nude mice accept allografts (no T cells due to genetic modification resulting in absent thymus)
  - B cell deficient mice reject allografts

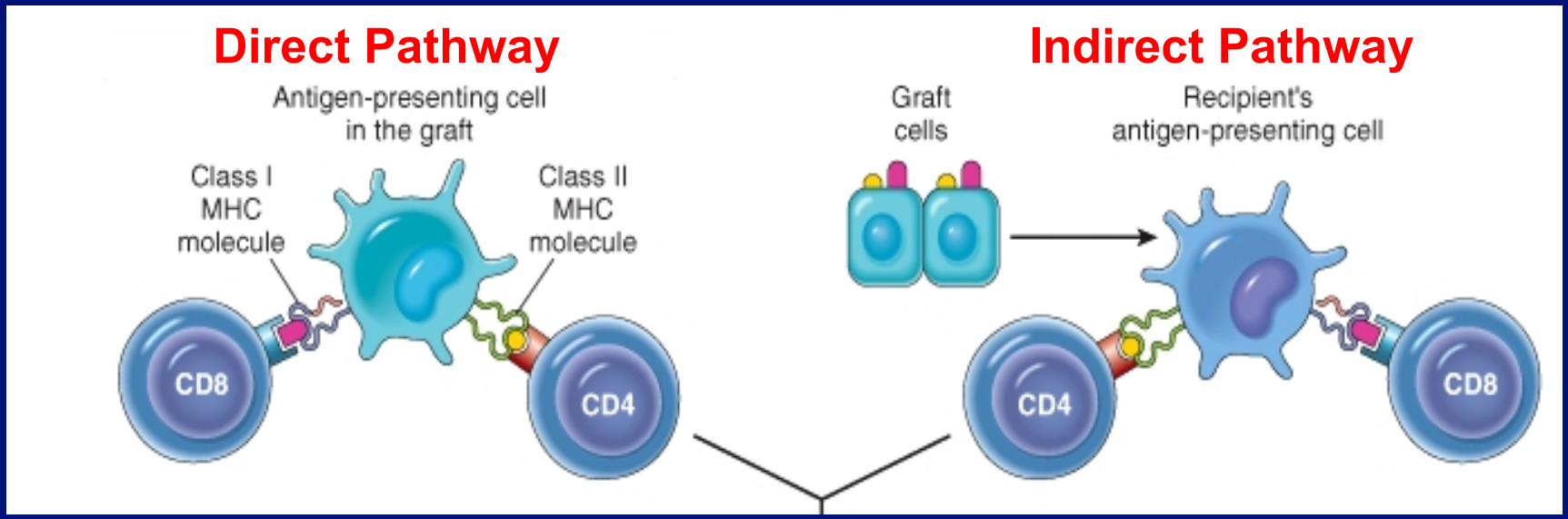
Nude mouse has a transplant of rabbit skin

Role of $CD4^+$ versus $CD8\ T^+$ cells

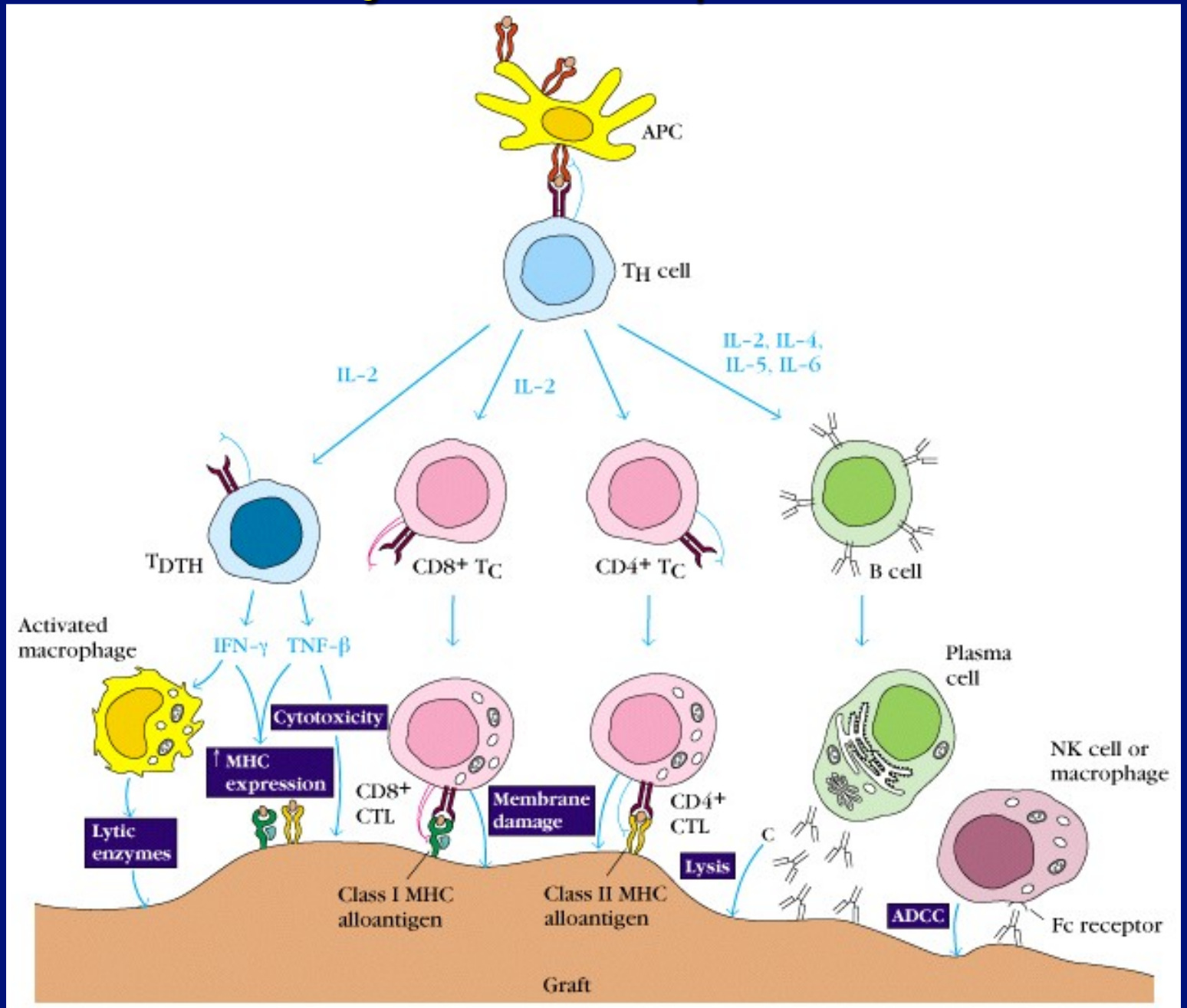


Injecting recipient mice with monoclonal antibodies to deplete one or both types of T cells

Mechanisms involved in Graft Rejection



Rejection Response

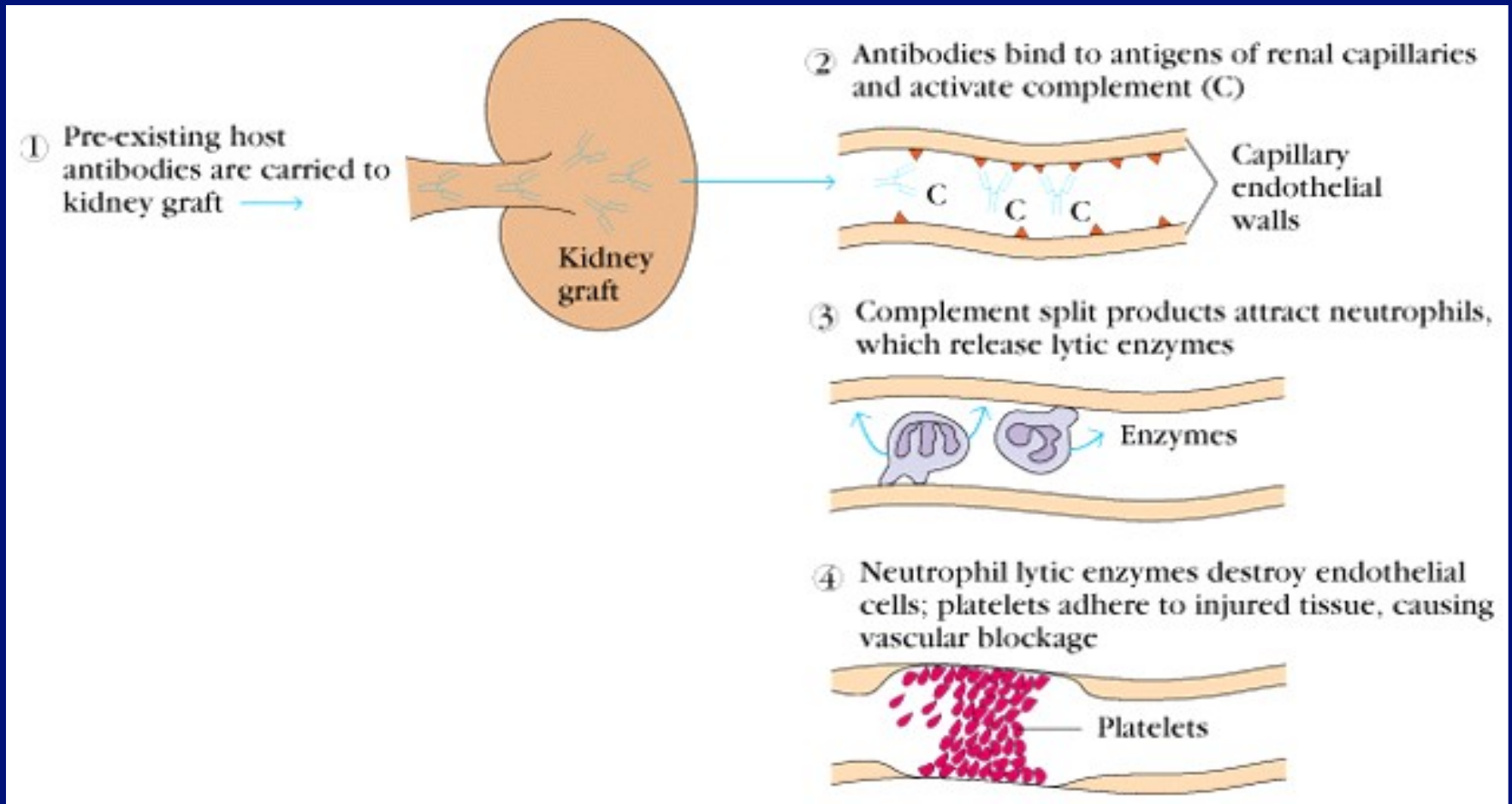


Clinical manifestations of graft rejection

I. Hyperacute rejection: very quick

II. Acute rejection: about 10 days (cell mediated)

III. Chronic rejection: months-years (both)



Chronic Rejection

- This occurs months to years after engraftment
- Main pathologic finding in chronic rejection is atherosclerosis of the vascular endothelium
- Main cause of chronic rejection is not known
  - Minor histo-compatibility antigen miss match

Graft-versus-Host (GVH) Reaction

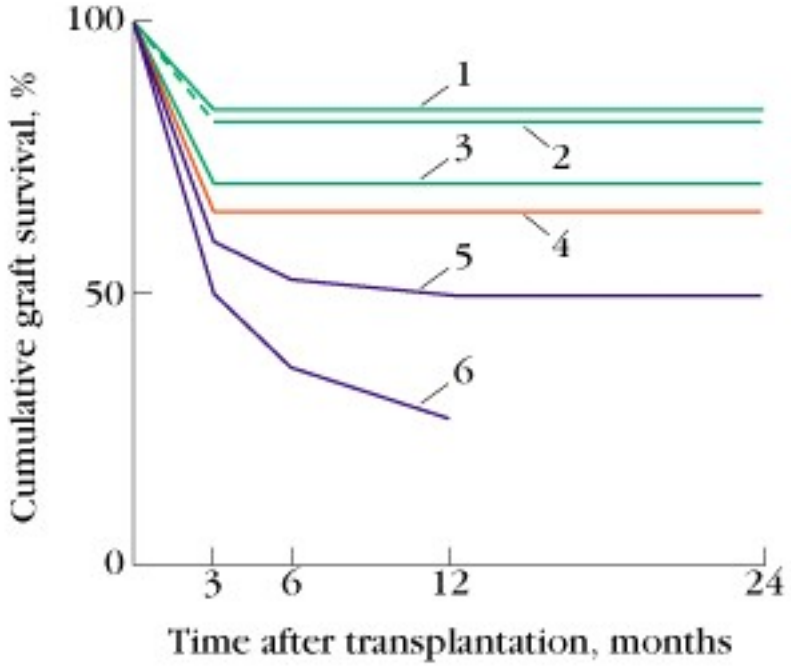
- Occurs in about two thirds of bone marrow transplants
- Occurs because grafted immunocompetent T cells proliferate in the irradiated immunocompromised host and reject cells with foreign proteins resulting in sever organ dysfunction
- Donor's Tc cells play a major role in destroying the recipient's cells
- Symptoms are: maculopapular rash, jaundice, hepatosplenomegaly and diarrhea
- GVH reactions usually end in infections and death

HLA Typing in the Laboratory

- Prior to transplantation laboratory test commonly called as ***HLA typing* or *tissue typing*** to determine the closest MHC match between the donor and recipient is performed
- Methods
  - DNA sequencing by Polymerase Chain Reaction (PCR)
  - Serologic Assays
  - Mixed Lymphocyte Reaction (MLR)
  - Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.

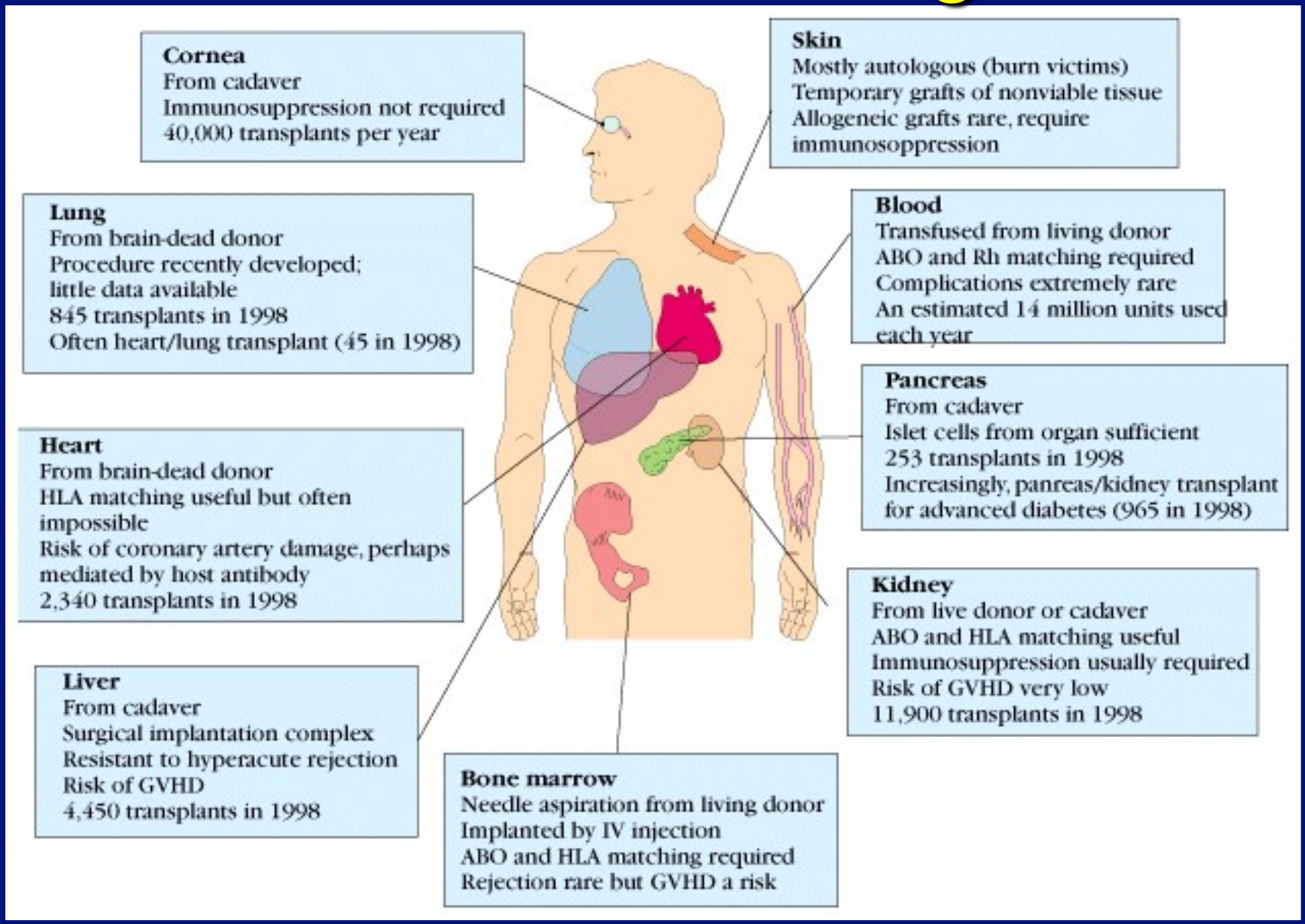
Tissue Matching

Effect of HLA class I & II matching on survival of kidney grafts



	HLA mismatches (no.)	
Curve no.	Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2

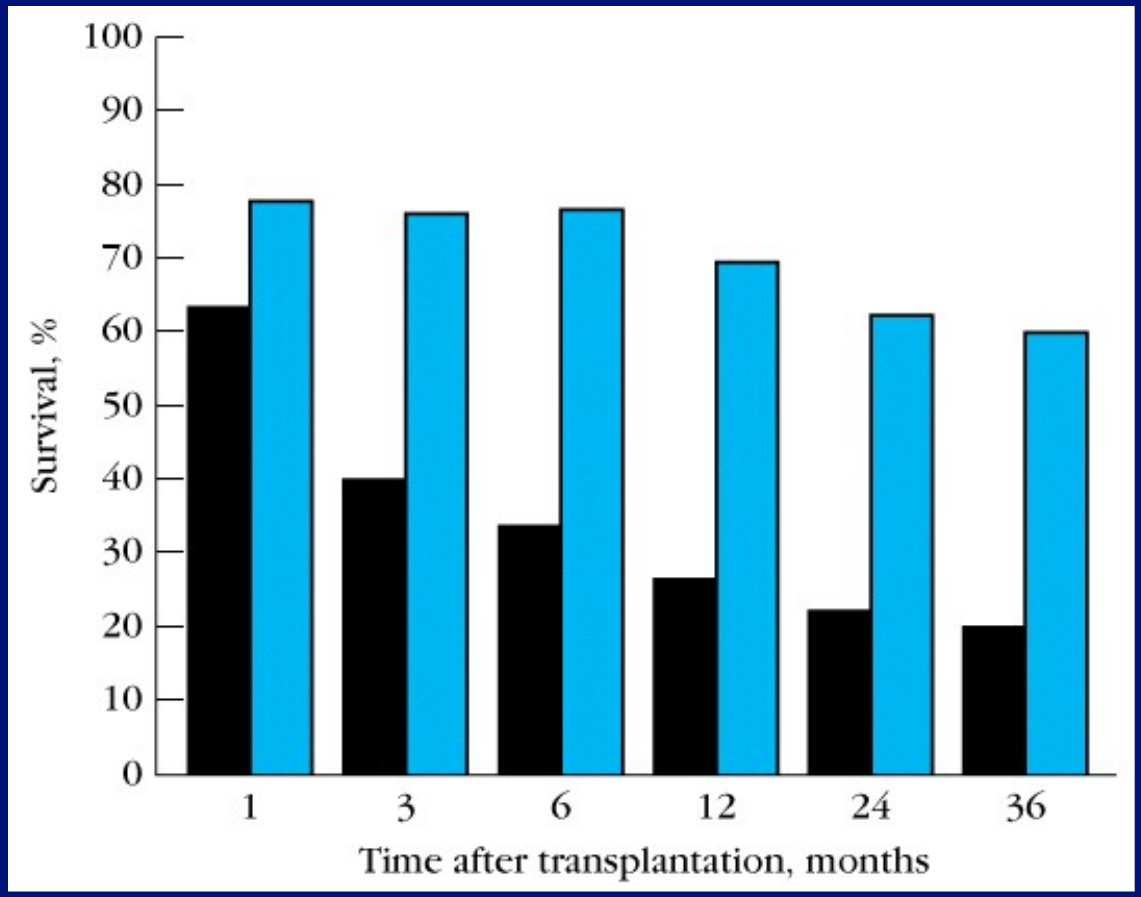
Tissue Matching



General Immunosuppression Therapy

1) Mitotic inhibitor: azathioprine (pre & post)
2) Corticosteroids
3) Cyclosporin
4) Total lymphoid irradiation

Immunosuppresive Therapy

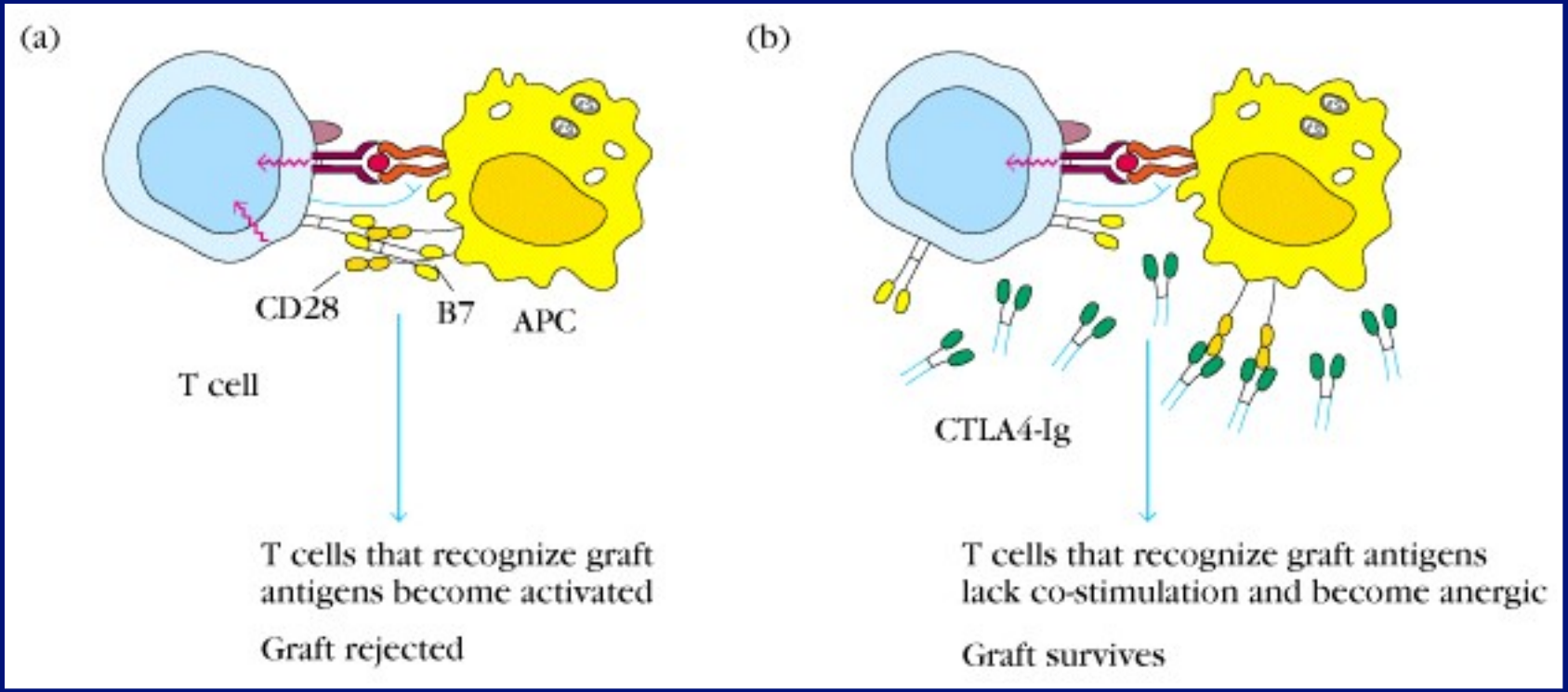


Comparison of the survival rates of liver transplants following azathioprine versus cyclosporin A treatment. Transplant survival rates are shown over a 3-year period for 84 liver transplant patients immunosuppressed using a combination of azathioprine plus corticosteroids (black) compared with another 55 patients treatecompared with another 55 patients treated with cyclosporin A plus corticosteroids (blue). [Sabesin SM, Williams JW. 1987. Current status of liver transplantation. Hospital Practice 22:75

Specific Immuno-suppression therapy

a) Monoclonal antibodies against T cell components or cytokines

b) Agents blocking co-stimulatory signal



Immuno-suppresive Therapy

- Downsides
  - Must be maintained for life
  - Toxicity
  - Susceptibility to infections
  - Susceptibility to tumors

Take home message

- HLA or MHC molecule miss-match can stimulate humoral and cell mediated immunity which is the main cause of rejection of transplants
- Cell mediated immune responses play a major role in transplant rejection
- Tissue matching particularly for HLA-D antigens is important for successful transplantation
- Immuno-suppresive therapy is usually required after transplantation

Thank you