Transplantation rejection

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Types of graft

Autograft

Garft in the same person from one part of body to other area like:

1. Skin graft
2. Hairs transplantation
3. Bone

Isograft

Between the identical twins

Allograft

This is between different members of the same species like:

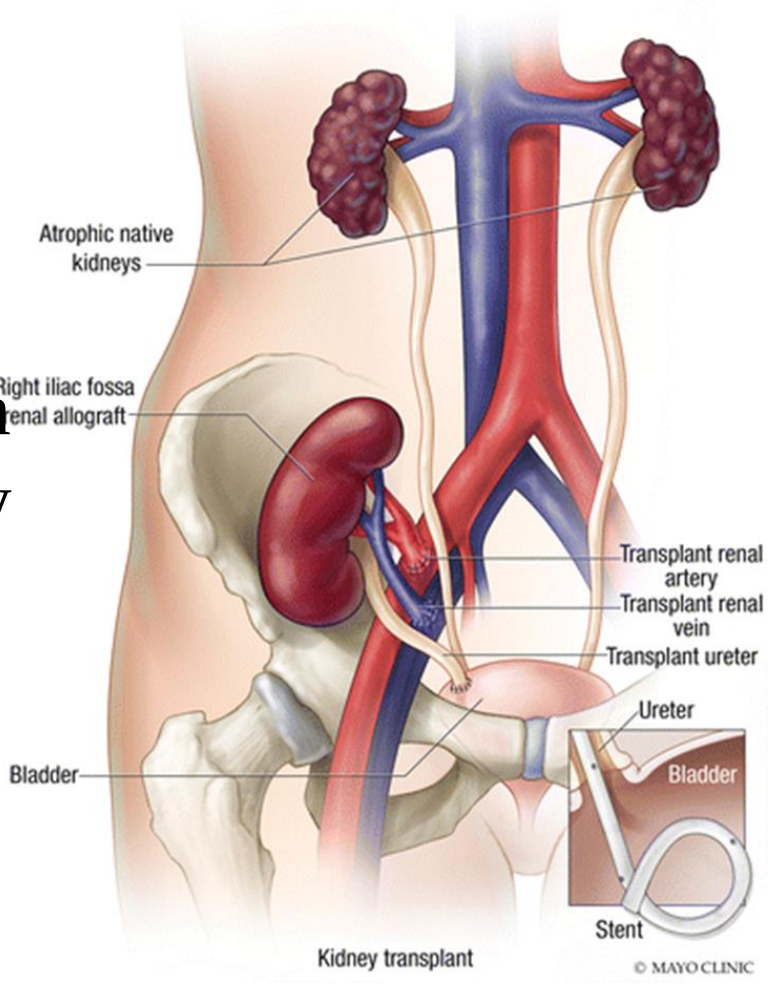
1. Kidney transplantation
2. Heart
3. Lung
4. Liver

Xenograft

Between two different species Like monkey to man

Types of transplantation

- Orthotopic graft: Donor organ transplanted to the diseased organ site- **liver**.
- Heterotopic graft: Donor organ transplanted at a site different from normal anatomical position Kidney in iliac fossa.
- Artificial (hybrid) organ implantation: Bio-artificial organs (combination of biomaterials & living cells)- experimental technique



The different types of grafts described have varying risks for rejection.

- The degree and type of response vary with the

1. MHC type,
2. blood groups,
3. Type of the transplant.

Some sites, such as the eye and the brain, are immunologically privileged (e.g. they have minimal or no immune system cells and can tolerate even mismatched grafts).

- Skin grafts are not initially vascularized and so do not manifest rejection until the blood supply develops.
- The heart, kidneys, and liver are highly vascular organs and lead to a vigorous cell mediated response in the host.

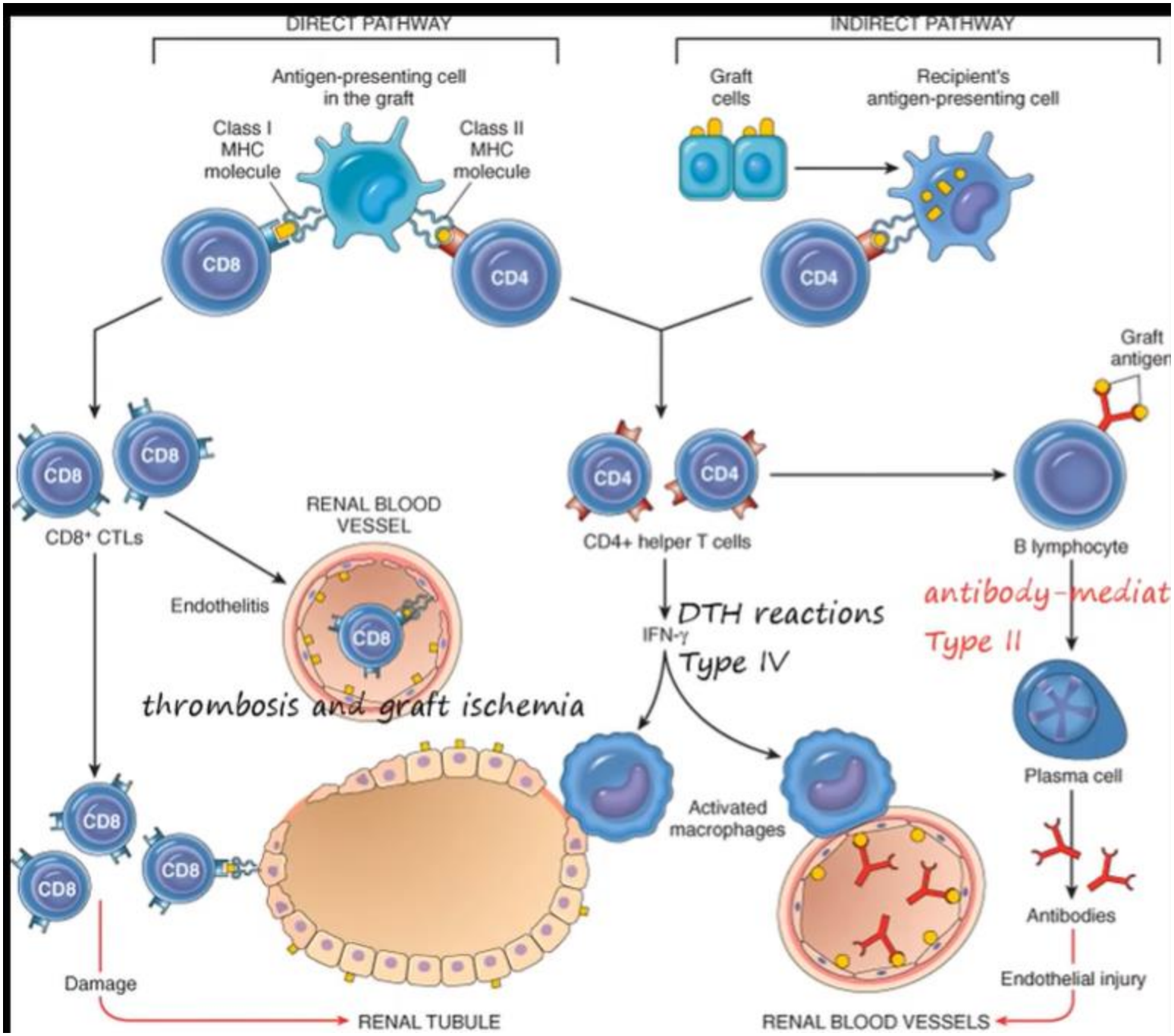
- Major antigens that cause rejection;
  - Blood group antigens
  - HLA antigens (MHCAgs)
- The number and variety of histocompatibility antigens tell us that probably no two humans (again, except for identical twins) exist on earth with perfectly compatible tissues and, so.
- Successful transplantation of allografts requires some degree of immunosuppression to avoid graft rejection.
- The immune response include cell-mediated (late) or antibody mediated (early).

Molecular mechanisms of graft rejection
Direct and indirect allograft recognition

- **Direct**; Initial studies showed that the T cells of a recipient graft recognize antigen on intact, unprocessed MHC molecules on the graft APC, the most strong reaction in acute rejection and short lived.
  - MHC2 or 1 on APC of donor present antigen to CD4 and CD8 in recipient
  - CD4 primed to TH1
  - CD8 activation by MHC1 (intracellular antigen)
  - macrophage and NK activation
  - and increase in IL-2 and IFN gamma cytokines.
  - cause tissue damage by Type 4 hyper sensitivity reaction.

Follow

- **Indirect**; recipient T cell recognize donor MHC processed by recipient APC and presented on recipient MHC ; in chronic or late rejection. Last long
- Indirect presentation may result in recognition by CD4+ T cells because donor antigen (Alloantigen) is acquired by host APCs primarily through the endosomal vesicular pathway (i.e., as a consequence of phagocytosis) and is therefore presented by class II MHC molecules.
- CD4 T cells provide help to B cells for antibody production which kill the graft by activation the complement cascade
- antibody-mediated damage


DIRECT PATHWAY
INDIRECT PATHWAY
Antigen-presenting cell in the graft
Class I MHC molecule
Class II MHC molecule
Graft cells
Recipient's antigen-presenting cell
CD8
CD4
CD4
Graft antigen
CD8
CD8
CD8+ CTLs
RENAL BLOOD VESSEL
Endothelitis
CD8
thrombosis and graft ischemia
CD4
CD4
CD4+ helper T cells
B lymphocyte
antibody-mediat
Type II
DTH reactions
IFN-γ
Type IV
Plasma cell
Activated macrophages
CD8
CD8
CD8
Damage
RENAL TUBULE
Antibodies
Endothelial injury
RENAL BLOOD VESSELS

Clinical stages of Allograft Rejection

- Hyperacute Rejection
- Secondary Rejection
- Acute Rejection
- Chronic Rejection

Hyper-acute Rejection

Hyperacute rejection is a severe and rapid form of graft rejection that occurs almost immediately upon transplantation.

- Hyperacute rejection is primarily associated with vascularized grafts, such as solid organ transplants (e.g., kidney, heart, lung) or vascularized composite allografts (e.g., hand transplants).

➢ **Pre-Existing Antibodies**: Type 2 hypersensitivity reaction

- The primary cause of hyperacute rejection is the presence of pre-formed antibodies in the recipient's blood against antigens on the surface of the transplanted organ.
- These antibodies are usually directed against human leukocyte antigens (HLAs), ABO blood group antigens, or other specific antigens expressed by the donor tissue.

➢ **Activation of the Complement System**: C3a, C5a

- Antibody binding to the vascular endothelium of the transplanted organ triggers the activation of the complement system.
- The complement cascade results in the formation of membrane attack complexes, which directly damage the endothelial cells of blood vessels within the graft.

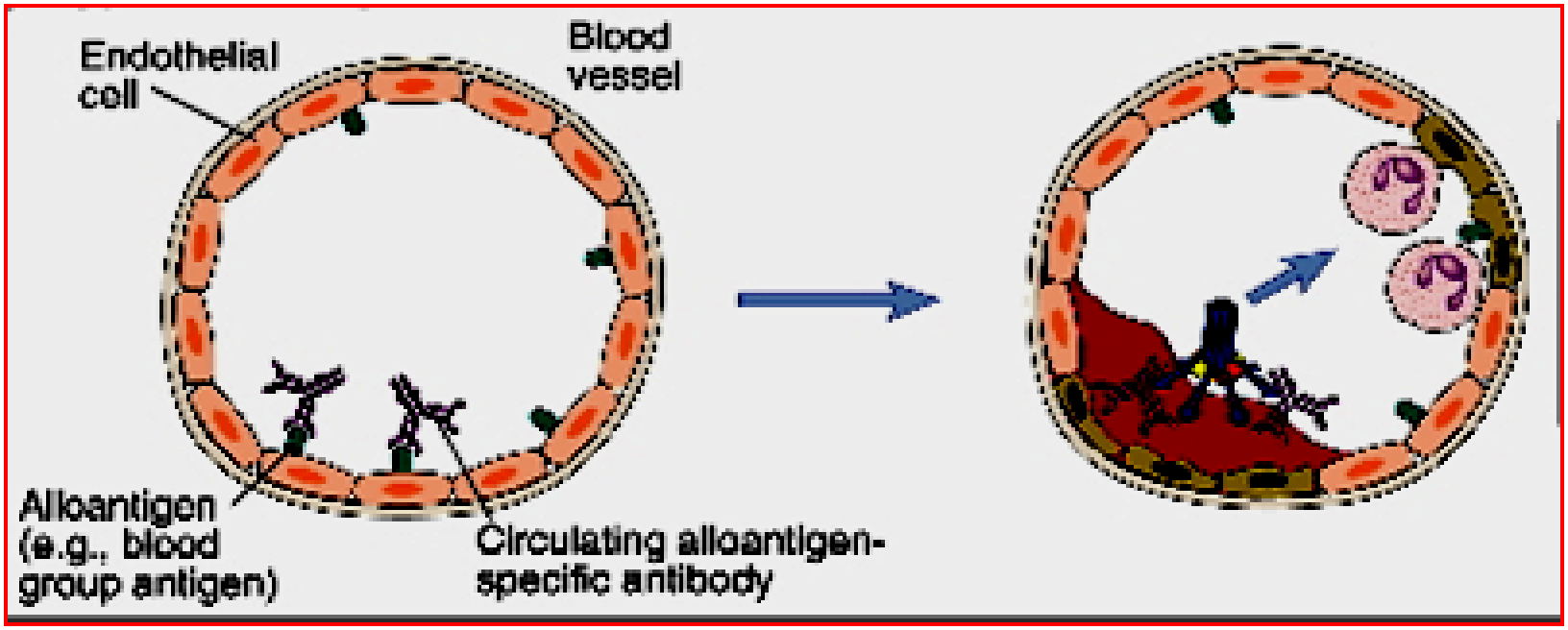
➢ **Ischemia and Thrombosis:**

- The complement activation and damage to the blood vessels lead to severe ischemia (lack of blood flow) and thrombosis (blood clotting) within the transplanted organ.
- This combination of events results in widespread tissue necrosis and organ failure.

➢ **Clinical Manifestations:**

- Hyperacute rejection is associated with a sudden and catastrophic loss of organ function.
- Clinical symptoms may include a rapid decline in organ function, severe pain at the graft site, and signs of organ failure.

Hyperacute Rejection



1. Preformed Ab, 2. complement activation,
3. neutrophil margination, 4. inflammation,
5. Thrombosis formation

Accelerated or secondary rejection

- HLA mediated
- This rejection is considered a subtype of acute rejection and occurs days to weeks after transplantation.
- It is due to presence of memory T-lymphocytes during the first graft rejection.
- Inflammatory Response: Accelerated rejection is mediated by, activation of monocytes and macrophages, and induction of cytotoxic lymphocytes from memory cells.
- Type 4 hypersensitivity reaction.

Acute Rejection

- Acute rejection typically occurs within the first few months after transplantation, but it can happen at any time. Usually begin within 3 mon (1-3 weeks) of transplantation. Due to tissue incompetability.
- **Immunological Mechanisms:**

Involves the activation of both cellular and humoral components of the immune system.

- **Cellular Rejection:** T cells play a central role. CD8+ cytotoxic T cells directly attack and damage the transplanted cells, while CD4+ T cells provide help and coordinate the immune response.
- **Humoral Rejection:** B cells may produce antibodies against donor antigens, contributing to rejection.

- **Cellular Infiltration:**

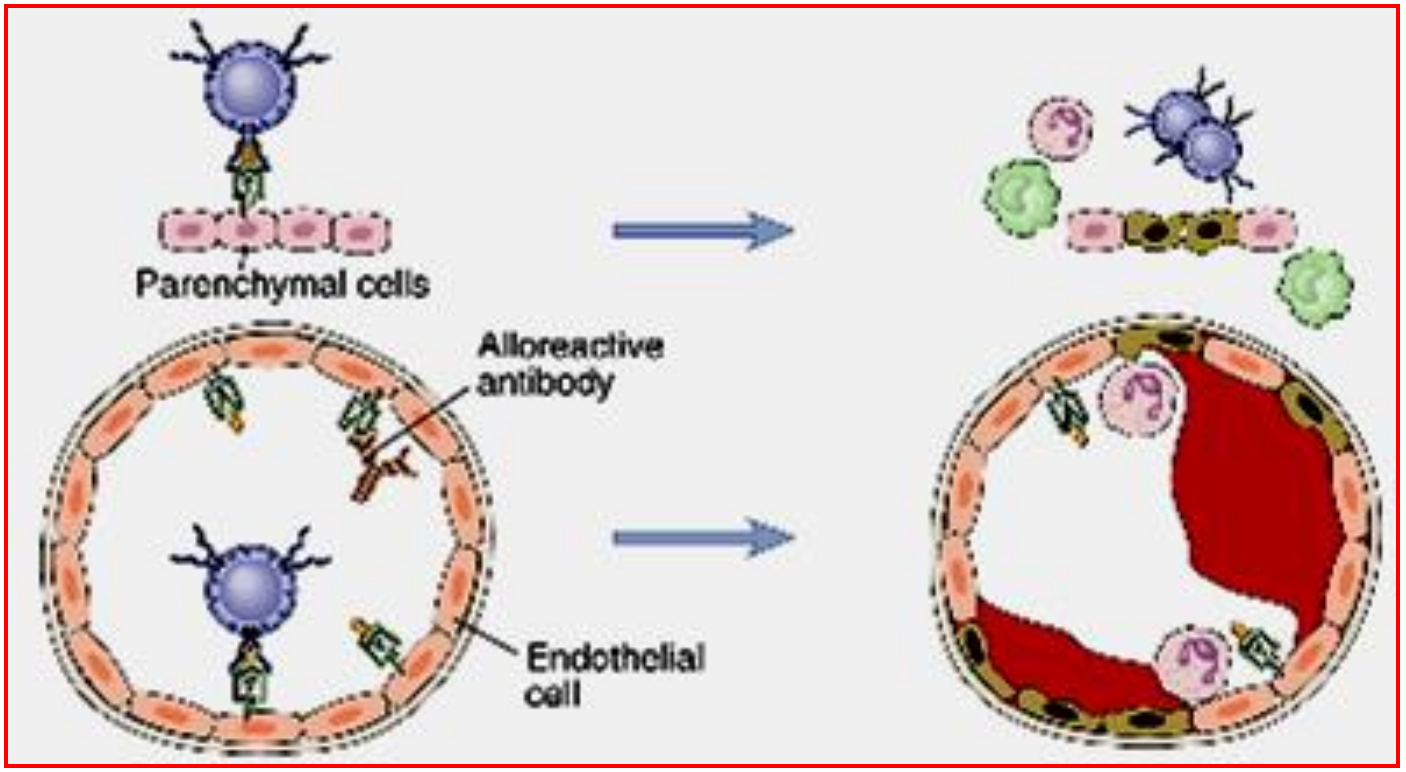
Immune cells infiltrate the transplanted tissue, leading to inflammation and tissue damage.

Infiltration is often observed in the blood vessels of the transplanted organ.

Vascular Injury:

Acute rejection can involve injury to the blood vessels within the transplanted tissue, contributing to ischemia and tissue damage.

Acute Rejection

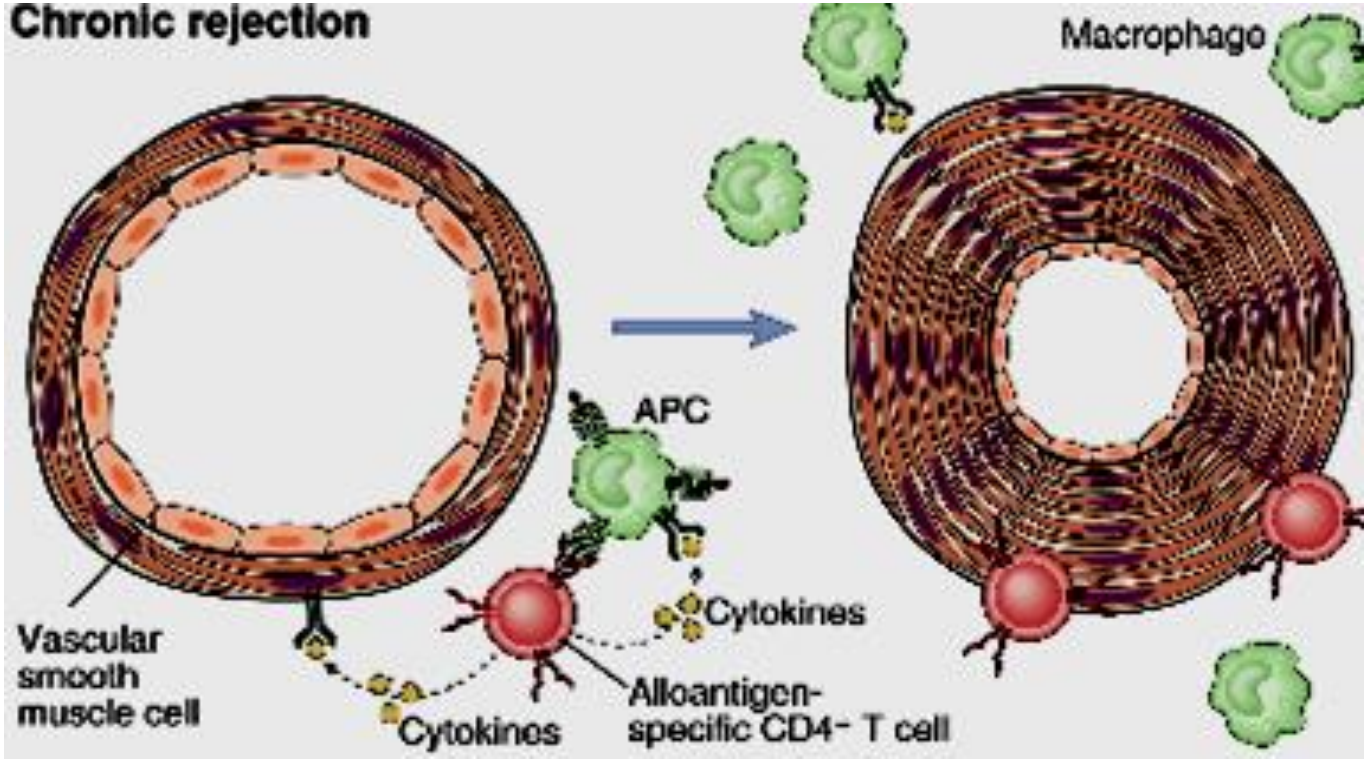


1. T-cell, macrophage and Ab mediated,
2. Endothelial and parenchymal injury,
3. Inflammation at site of rejection

Chronic Rejection

- Chronic rejection is characterized by the gradual and irreversible deterioration of the transplanted organ over an extended period.
- Occurs suddenly after months or years after frequent acute rejection episodes.
- Involves both humoral and cellular mechanisms.
- One of the hallmark features of chronic rejection is the development of fibrosis and scarring within the transplanted organ.
- Fibrosis leads to the replacement of normal functional tissue with non-functional scar tissue.
- Chronic rejection often affects the blood vessels supplying the transplanted organ, leading to a condition known as transplant vasculopathy or **chronic allograft vasculopathy** (**CAV**), which is gradual narrowing and occlusion of blood vessels, compromising blood flow to the organ.
- The use of immunosuppressive drugs and tissue-typing methods to prevent acute rejection, and treat any risk factors has increased the survival of allografts to delay chronic rejection but it is not prevented in most cases.

Chronic Rejection



1. Macrophage – T cell mediated and antibody mediated
2. Concentric medial hyperplasia
3. Chronic delayed type hypersesitivity reaction

The following factors increase the risk of chronic rejection:

- Repeated episodes of acute rejection.
- Inadequate immunosuppression
- Donor-related factors (eg, old age, hypertension)
- Ischemia-Reperfusion Injury.
- Recipient-related factors (eg, diabetes, hypertension, hyperlipidemia)
- Certain viral infections, such as **cytomegalovirus** (CMV), can contribute to chronic inflammation and immune activation.

Bone Marrow Transplantation

- Also known as hematopoietic stem cell transplantation (HSCT). Derived from bone marrow, peripheral blood, or umbilical cord blood.
- Used for treatment of Leukemia, Anemia and immunodeficiency, especially severe combined immunodeficiency (SCID).
- Recipient of a bone marrow transplant is immunologically suppressed before grafting, e. g; Leukemia patients are often treated with cyclo-phosphamide and total body irradiation to kill all cancerous cells.
- Because the donor bone marrow contains immunocompetent T cells, the graft may reject the host, causing graft versus host disease (**GVHD**).

Graft vs. Host Disease

Main complication of bone marrow transplant

- However, graft-versus-host disease can occur in those received stem cells/bone marrow from an HLA matched donor. HLA-identical donors often have genetically different proteins (called minor histocompatibility antigen)
- **Acute GVHD <100 day**
  - Characterized by epithelial cell death in skin rash, GIT nausea vomiting, and liver; yellow discoloration.
- **Chronic GVHD > 100 days**
  - Characterized by atrophy and fibrosis of one or more of these same target organs

Minor histocompatibility Ags

- **Minor histocompatibility antigens** (mHAgs)
  - **H-Y**, an antigen encoded on the Y chromosome and thus present in male, but not female tissue
  - **HA-2**, an antigen derived from the contractile protein myosin.

Treatment of GvH disease

- Injecting donor graft with mono-clonal antibodies to inhibit T cells,
- Increase immunosuppressive drugs to the recipient.
- **Grafts that are not rejected**
  - Privileged sites. These include the **brain**, anterior chamber of the **eye**, **testis**, **renal** tubule, **uterus**,
  - **Sperm**
  - **Pregnancy**, trophoblast cells not expressing MHC, immunosuppressive hormones produced by fetus (estradiol, progesterone), immunosuppressive layer covered the fetus, blocking antibodies

Pretransfusion compatibility testing
Prevention of graft rejection

- Evaluation of the donor includes
  - Testing of the donor unit for infectious diseases
  - ABO/Rh typing
- Evaluation of the recipient includes
  - ABO/ Rh typing
  - Antibody screen. Perform antibody identification if antibody screen is positive to determine the identity of the antibody,
- Crossmatch Tests the compatibility of the recipient's serum with RBCs from potential donor unit

❖**Tissue typing or HLA typing**

Identify MHC I & II for both donor & recipient

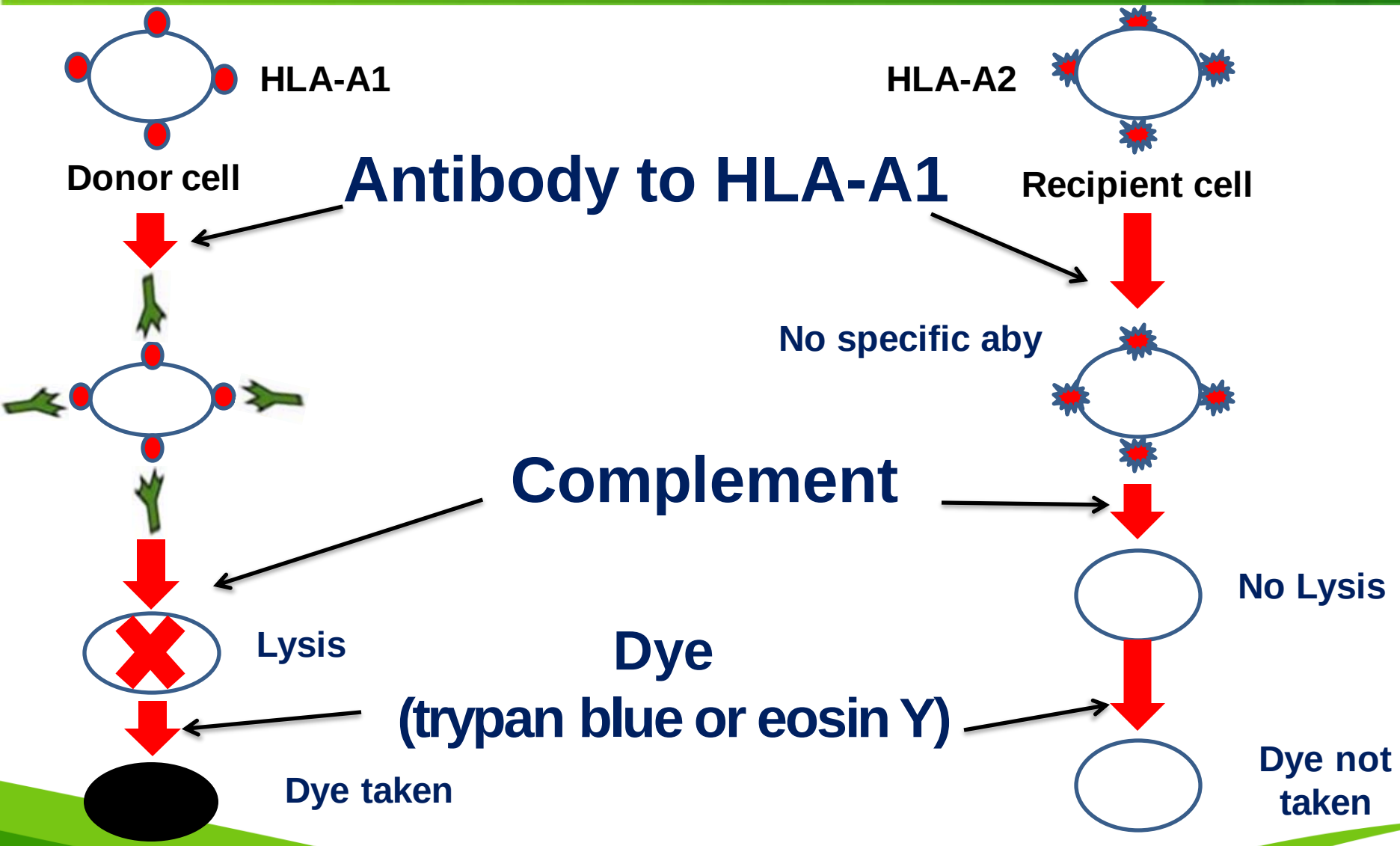
By:

A. Mixed lymphocyte reaction (MLR)

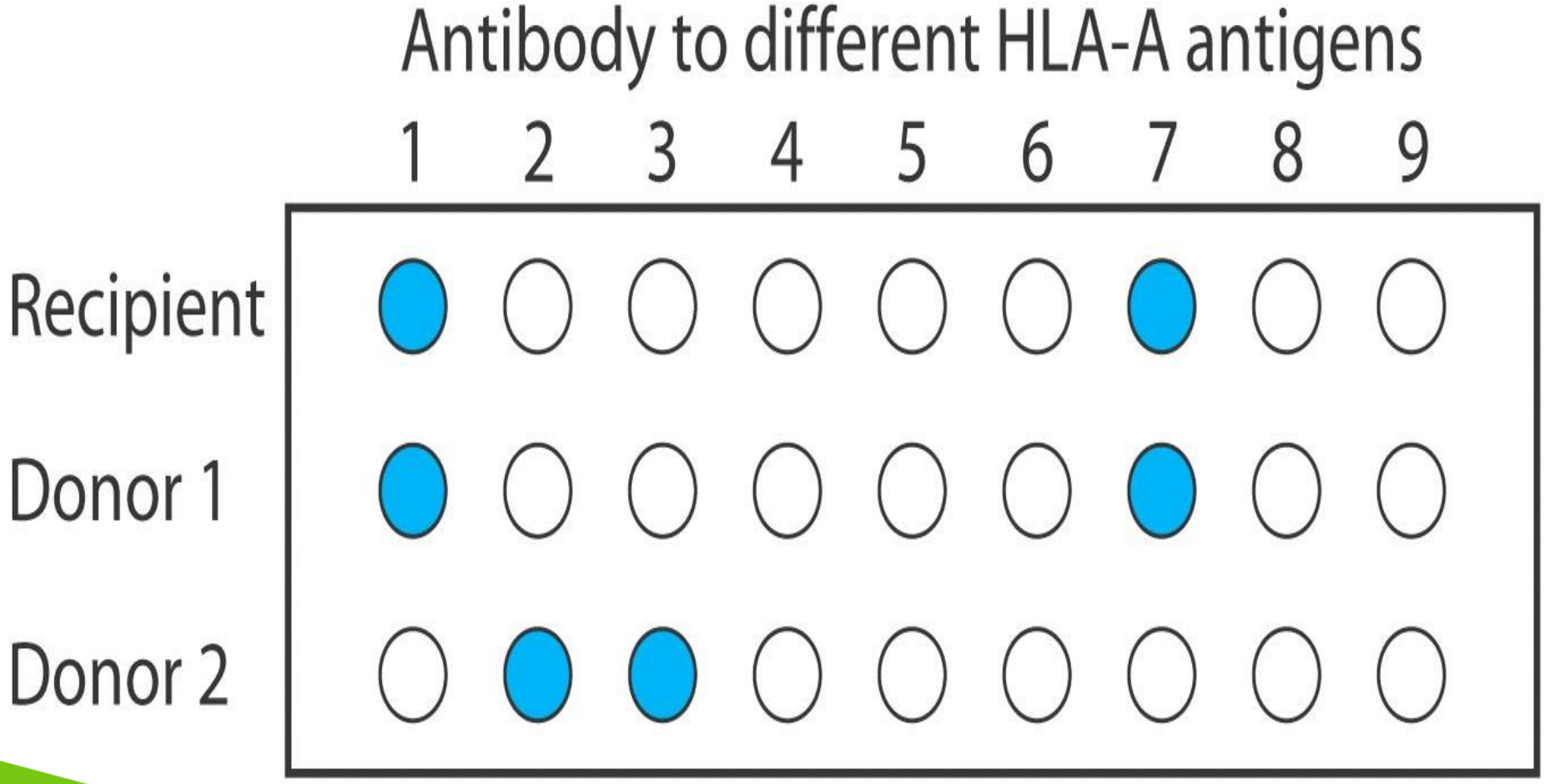
B. Lymphocytotoxicity assay.

C. Panel-reactive antibody (PRA) lab specialist will test a patient's blood (serum) against lymphocytes (white blood cells) obtained from a panel of about 100 blood donors. test that quantifies the risk of transplant rejection. A high PRA usually means that the individual is sensitized and high percentage of rejection may occur.

Lymphocytotoxicity test (serologic typing)

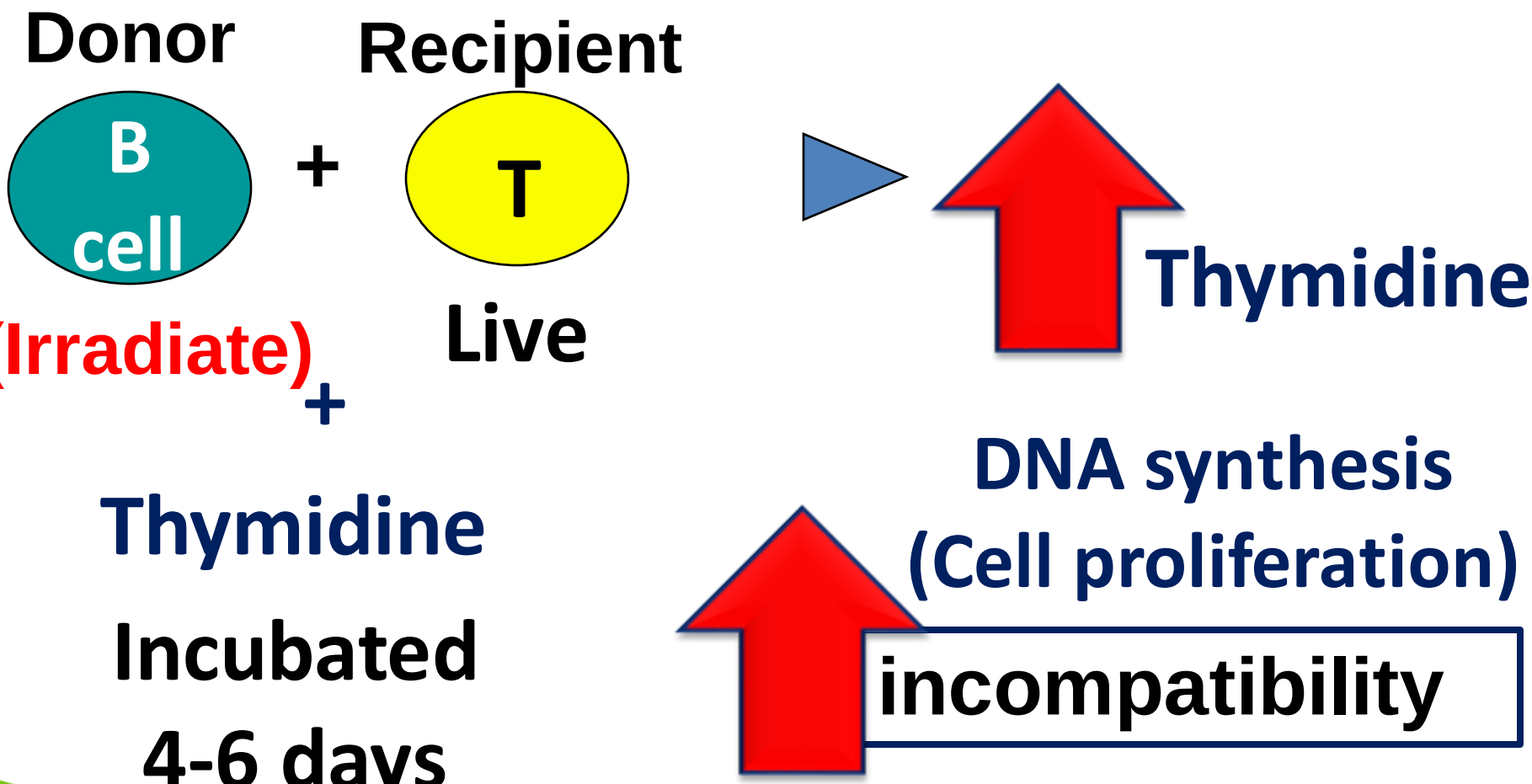


Lymphocytotoxicity test (serologic typing)



(MHCI & MHCII)

b- Mixed lymphocytic reaction (MLR)

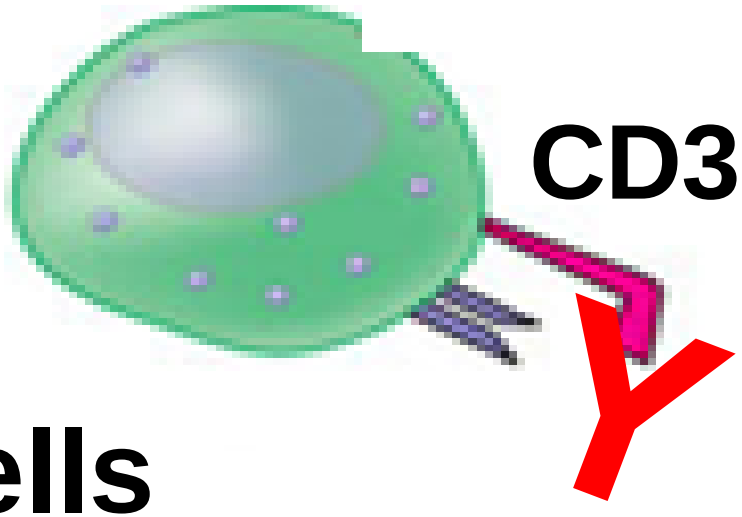


Immune-suppressive drugs

- Initially, radiation and chemicals were used as nonselective immunosuppressive agents
- **Corticosteroids**, inhibit immune response, it is a glucocorticoid-based medication that works principally to block T cell and APC derived cytokine. The major elements blocked are proinflammatory cytokines IL-1, TNF and IL-6.
- **Azathioprine**: antiproliferative (inhibit T cell proliferation).
- **Methotrexate**: Inhibit Immune cells growth (anti folate and inhibit DNA synthesis)
- Inhibitor of IL-2
  - **Calcineurin inhibitors** that inhibits calcineurin. This inhibition ultimately inhibits the production and secretion of IL-2 and prevent T cell activation and growth. e.g.;Cyclosporin antibiotic and tacrolimus
  - **Sirolimus**
- Antibodies
  - Anti-lymphocyte antibodies; anti-CD3
  - Two antibodies that are IL-2 receptor antagonists (basiliximab and daclizumab)

Monoclonal antibody

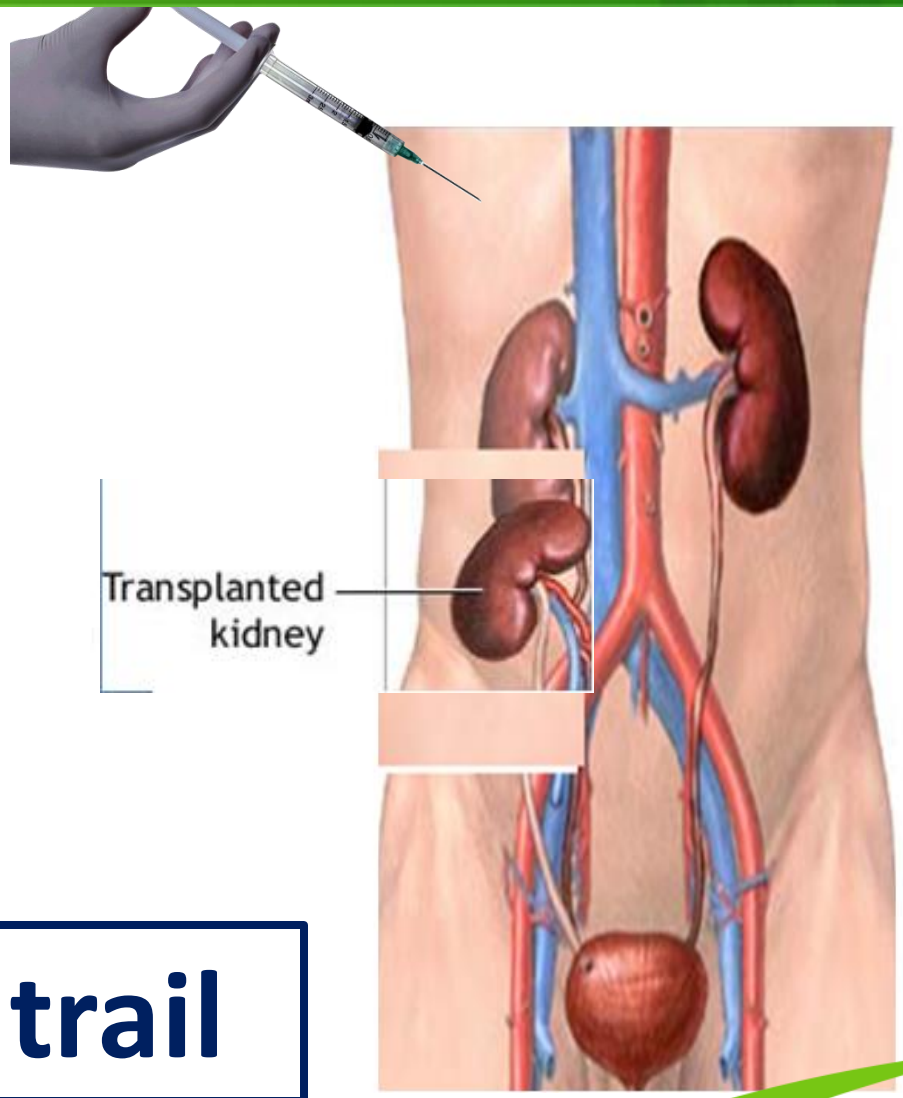
- **Use of Abs against T cell.**



Antigen specific induced tolerance

Low/high dose Ag

Become tolerant



Under trail