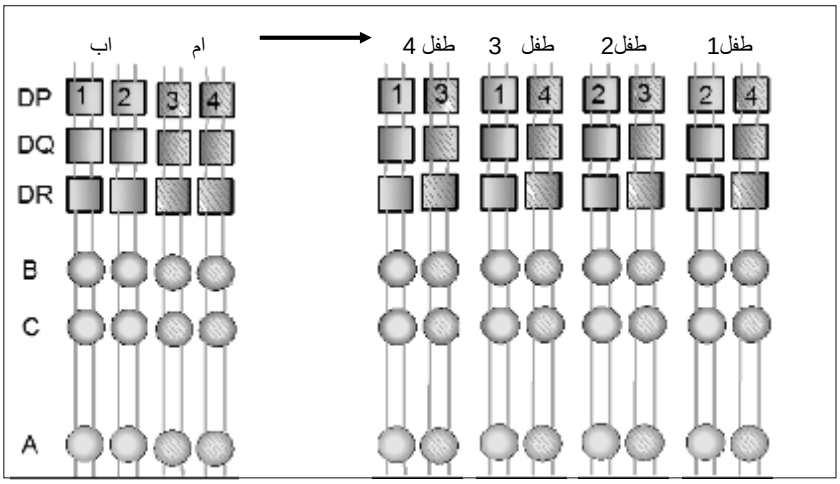
Transplantation and immune response

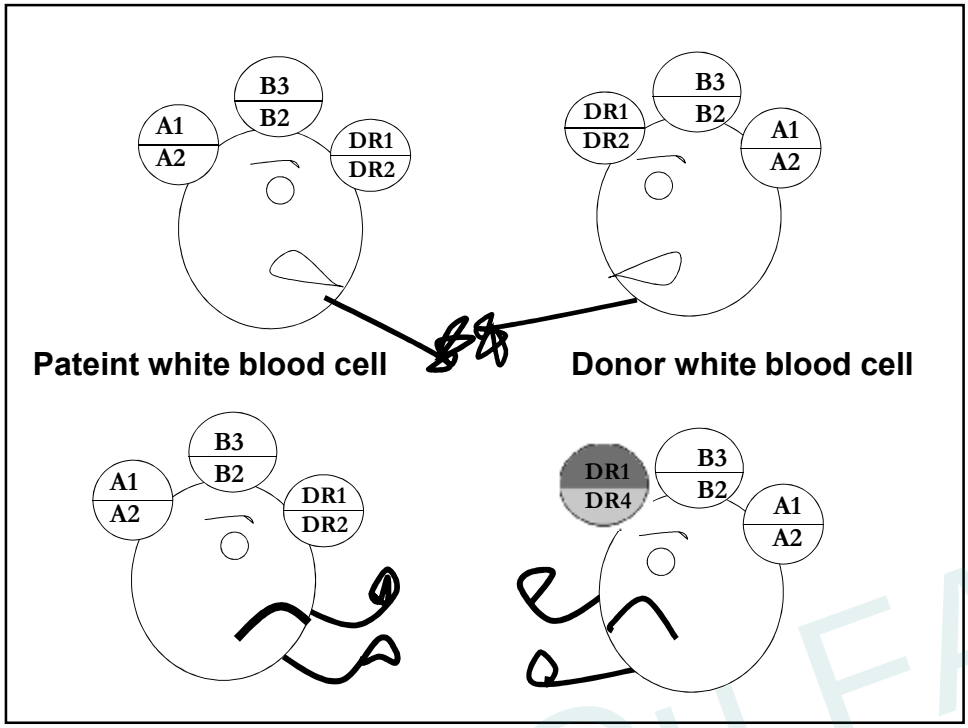
MHC Polymorphism

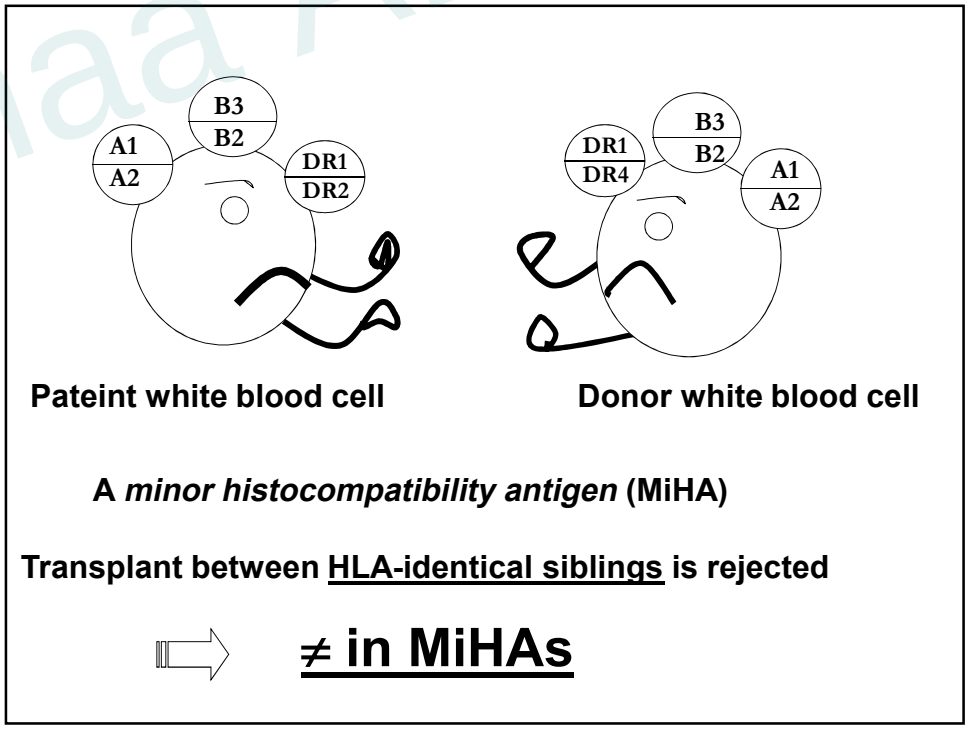
It is for this reason:

it is extremely difficult to match the donor and the recipient.

The inheritance of MHC genes







A *minor histocompatibility antigen* **(MiHA)**

Transplant between <u>HLA-identical siblings</u> is rejected

⇨ **<u>≠ in MiHAs</u>**

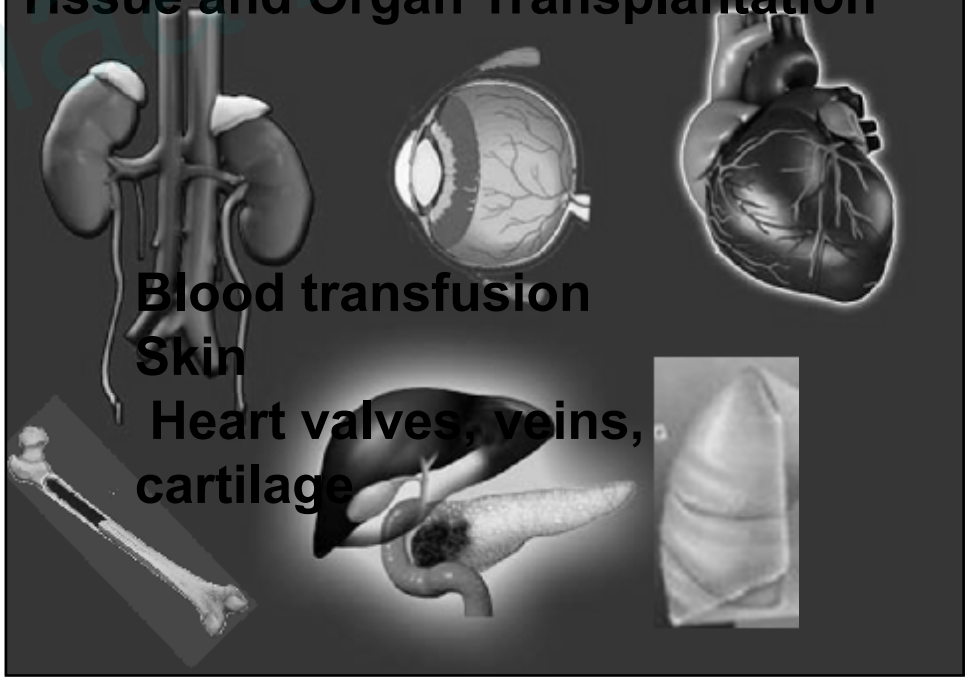
What are MiHAs?

MiHAs result from allelic variation in "housekeeping" genes.

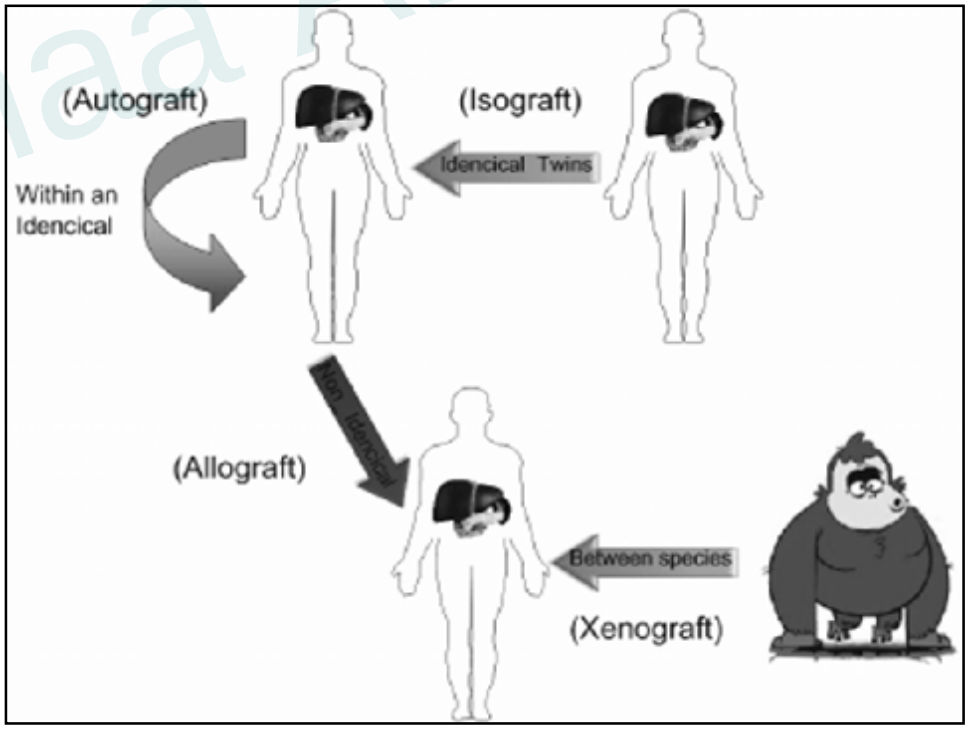
(genes encode proteins that maintain basal metabolic functions).

expressed in all cell types
very low polymorphism genes

Tissue and Organ Transplantation



Blood transfusion
Skin
Heart valves, veins, cartilage



Types of Transplant

➢**Autograft**
Self-tissue transferred from one body site to another in the same individual.

➢**Isograft**
Tissue transferred between genetically identical individuals.

➢**Allograft**
Tissue transferred between genetically different members of the same species.

➢**Xenograft**
Tissue transferred between different species

Kidney Transplantation

Diseases like diabetes and various type of nephritis

Heart Transplantation

Heart failure

Lung Transplantation

Cystic fibrosis and emphysema or acute damage to lungs

Liver transplantation

Congenital defects

Viral infection

Alcoholism, toxic

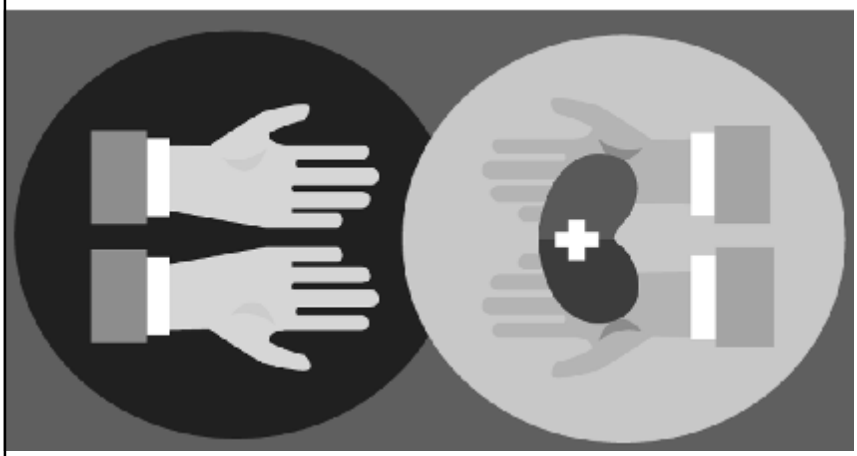
Pancreas Transplantation

Diabetes mellitus to prevent the typical diabetic secondary complications

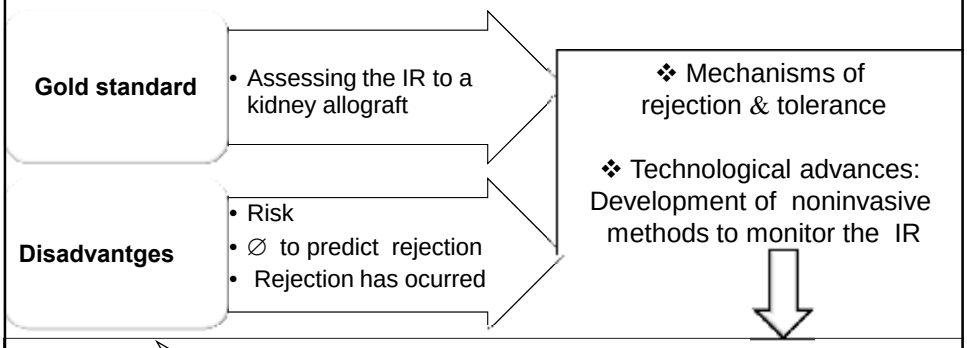
Skin grafting

Burn victims

When a patient gets a new kidney, there's no guarantee that the body will accept the foreign organ.



Renal biopsy



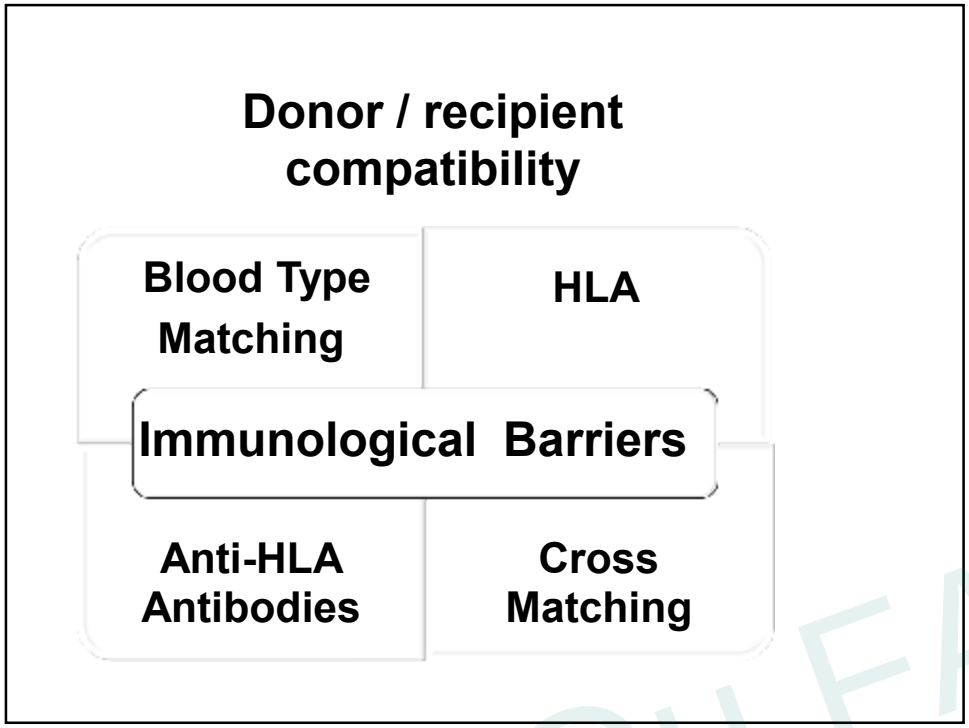
➢Improving risk-assessment strategies
➢Tailoring immunosuppressive therapies to target the specific mechanisms in each patient

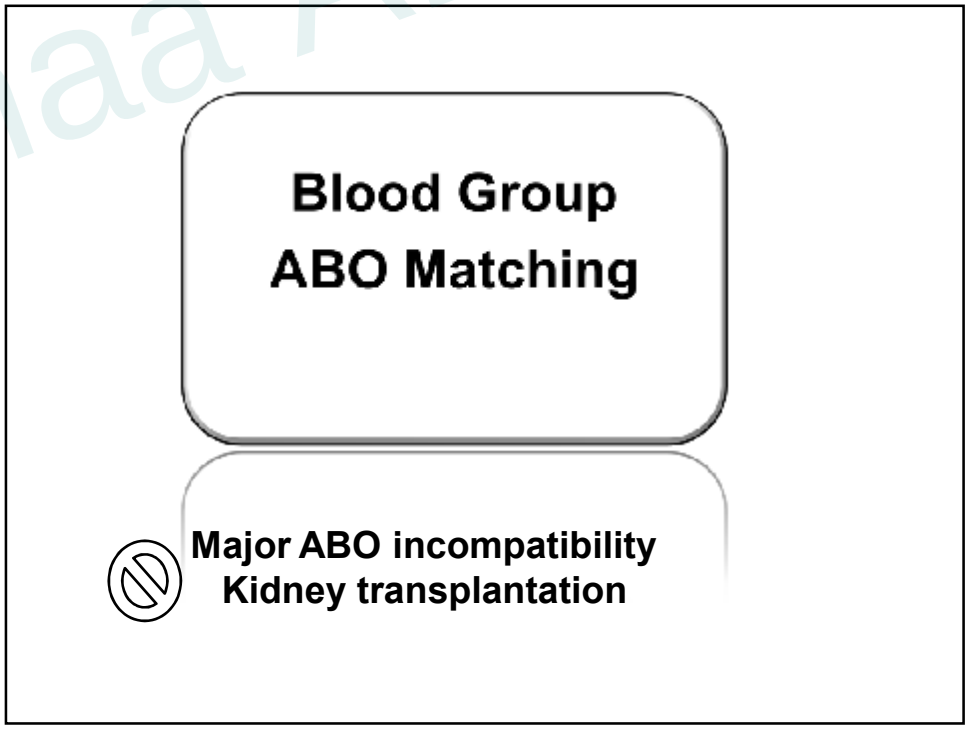
Improve patient outcome

Matching Recipient / Donors

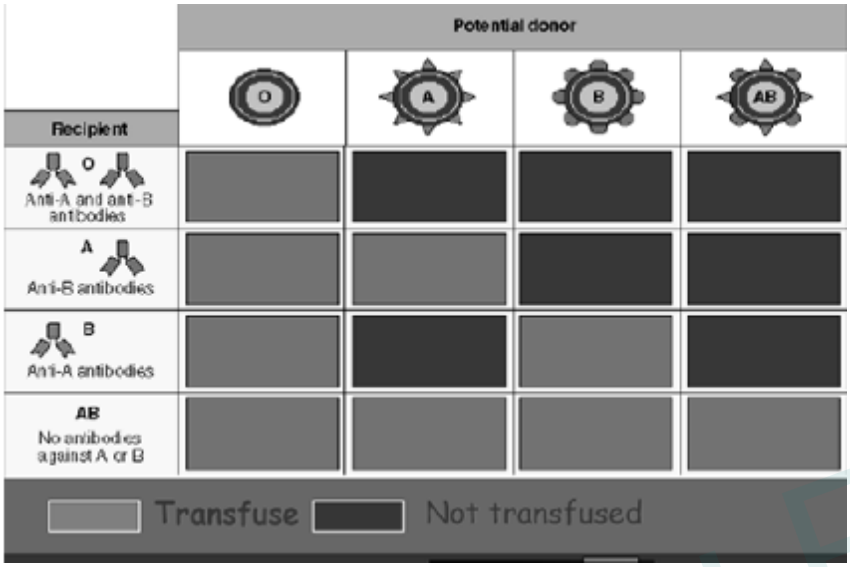
Donor(s)

- ❑ **Healthy**
- ❑ **Compatible**





Blood Type Compatibility



Desensitization

- The reduction and maintenance of anti-A/B Abs during the first 2w after transplantation(<1:8,tube technique).

  BTS and euorpean guidelines.

- ≈ 30% of living donors who can now donate their kidneys, expand the living donor pool.

- Anti-A/B Abs recur at high levels they will not harm the kidney transplant
- Accommodation:

resistance of an allograft to AMR, despite the presence of significant levels of anti-ABO antibodies and C4d deposition, differs from tolerance

Transplantation in the presence of major ABO incompatibility :
early rejection, infection,
infection-associated death.

whenever possible

HLA Matching

Hierarchical influence of HLA matching

- HLA-DR compatibility is most important in the first period after transplantation(less rejection),
- HLA-B and, to a lesser extent, HLA-A influence longer term transplant survival.
- HLA- **A+B+DR match**, or sometimes only an HLA- **B+DR match**.
- HLA-C: A significant influence only in situations in which additional HLA -B mismatches.
- HLA-DQ : Not established.
- HLA-DP: is currently out to consultation (Graft survival in re-graft recipients).

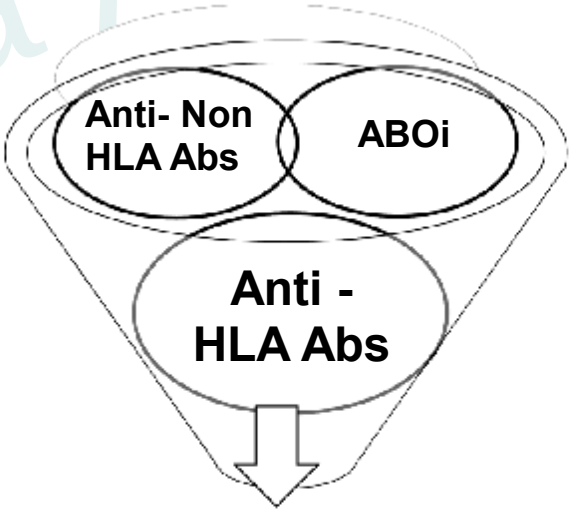
HLA match or not to match

- Better graft survival both for deceased or live donor transplants.
- Lower dosages of immunosuppressive drugs
- Lower grades of sensitization for re- transplants
- Reduced incidence of the de novo DSA development

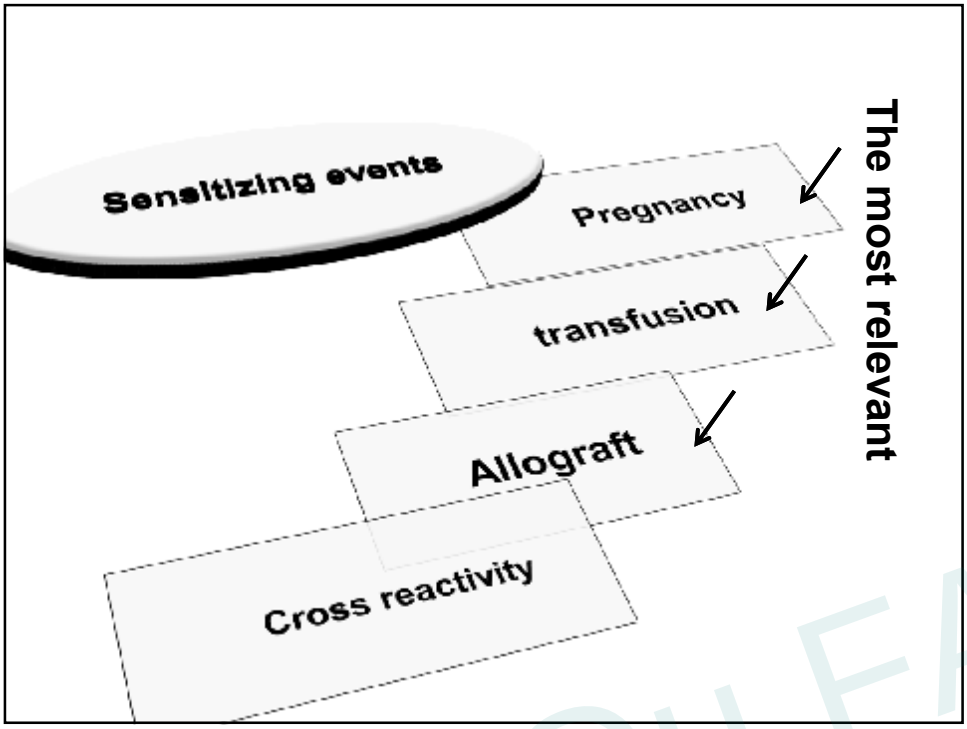
Anti-HLA anti-bodies

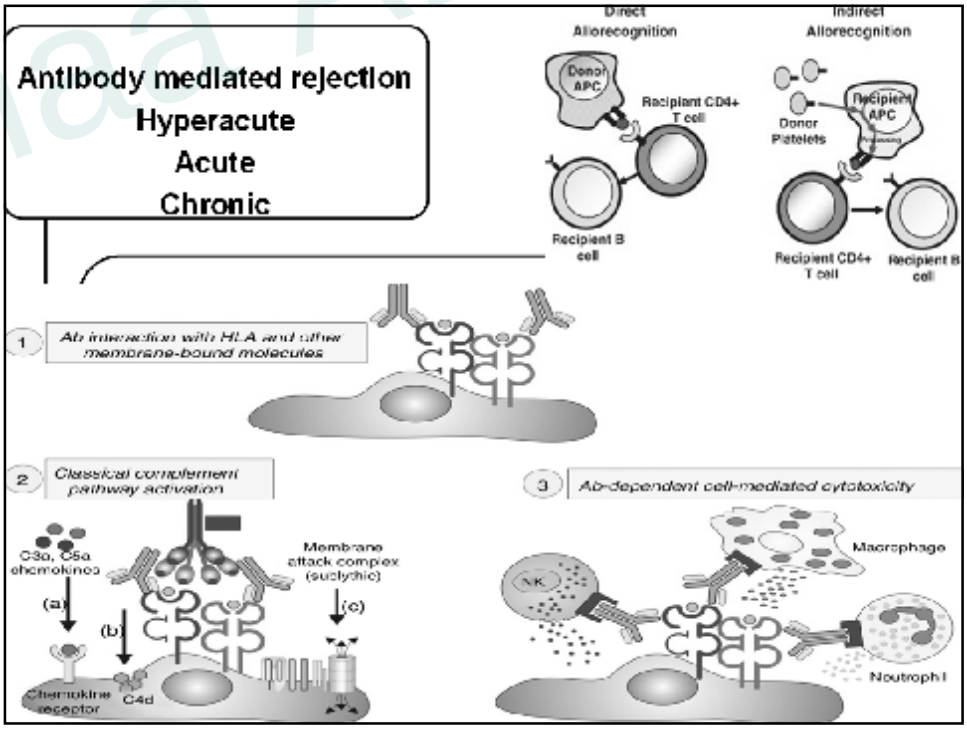
One of the most critical problems in organ transplantation

Detection of a circulating anti- HLA antibody is now a widely used immunologic monitoring assay



Sensitization
Transplantation in patients with anti-donor antibodies





Anti-HLA Abs definition

DSA: Donneur Specific Antibody

Preformed DSA: Significantly greater risk of having an hyperacute or acute rejection (AMR)

De novo DSA : Develop in post-transplant period, resulting in acute or chronic rejection. can be the first sign of ongoing damage in stable patients.

Serum screening When to do?

Pre-transplant

- Quarterly serum screening for patients awaiting renal transplantation.
- Samples should be submitted between 14 and 28 days following any known sensitising event
- Presence of HLA allo-Abs in a recipient correspond to ‘‘antibody defined unacceptable antigens’’ which are best avoided when selecting potential donor grafts.

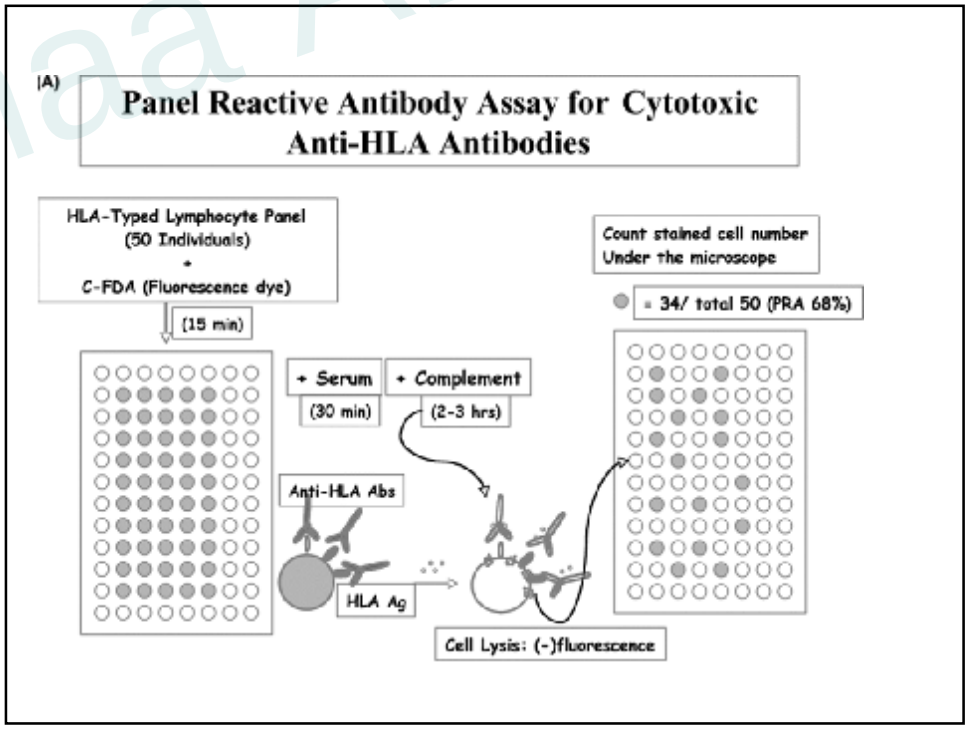
Post transplant

Panel Reactive Antibodies (PRA)

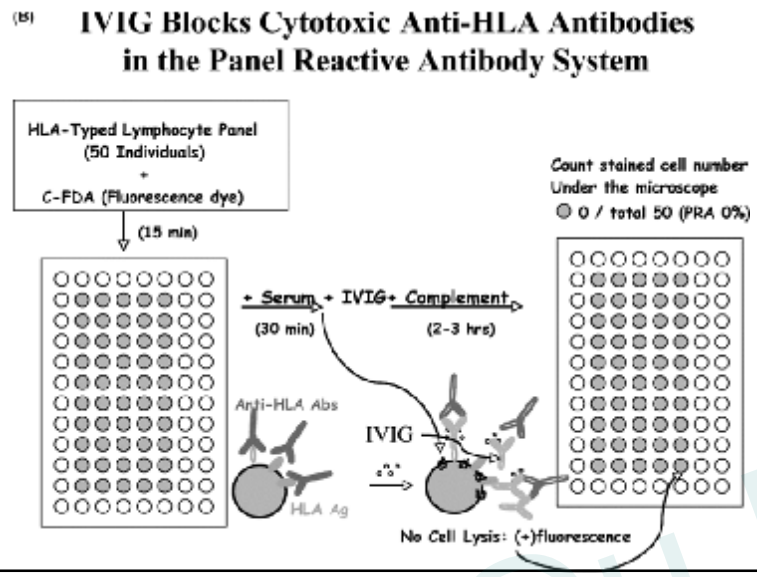
Measures the level of Abs in the recipients blood.

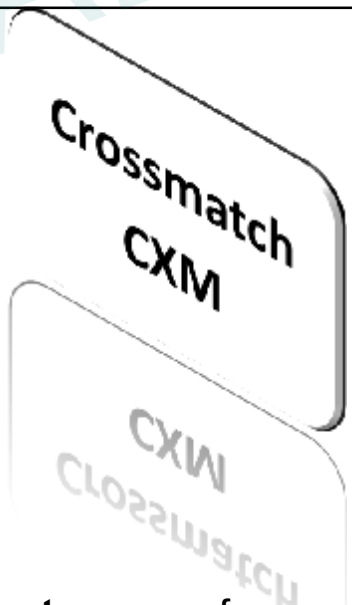
Represents the % of the population that the Abs in blood would react to and reject the kidney

≈ 20% of the people have high PRA's : limit the number of donors

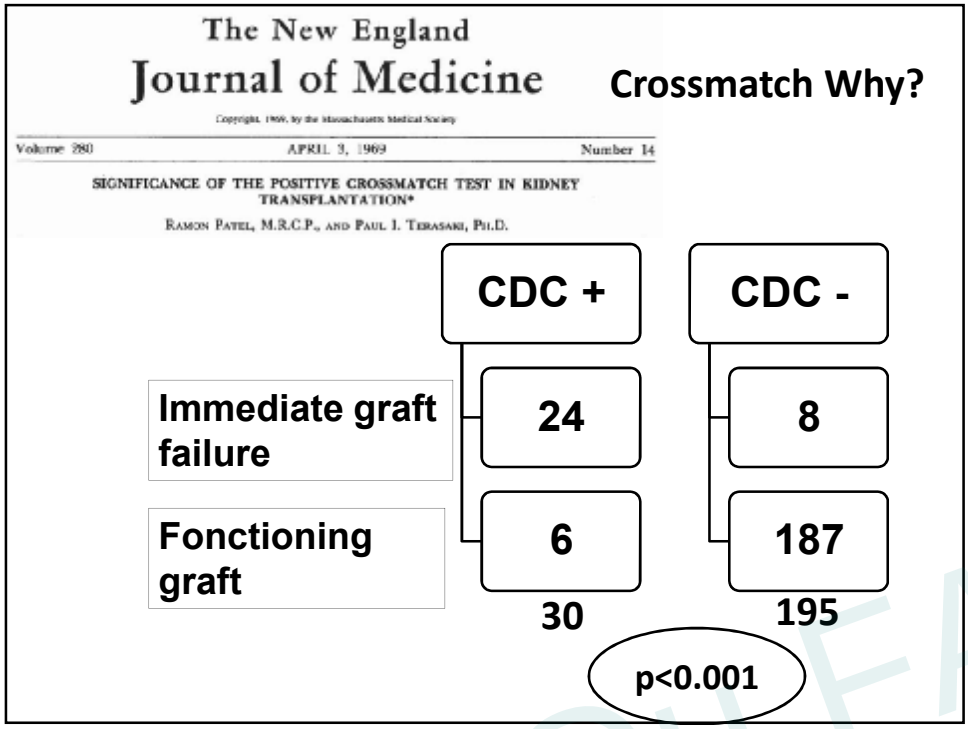


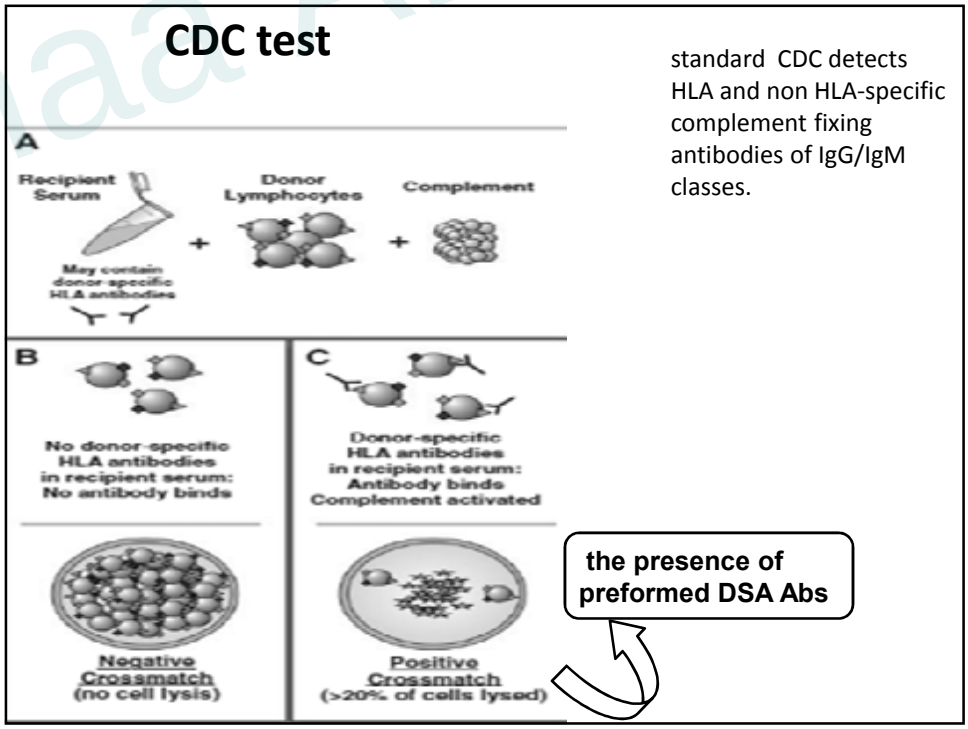
IVIG : improve transplant rates and outcomes in highly HLA-sensitized patients





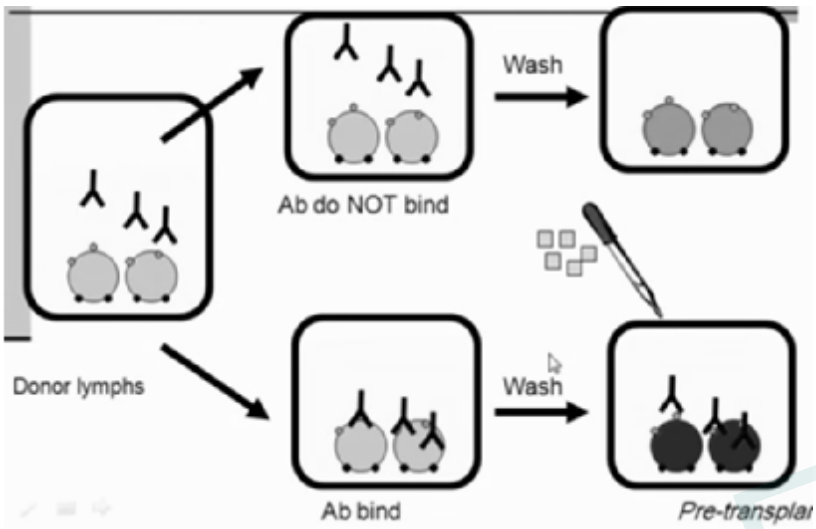
Tests **recipient serum** for pre -formed Abs against a single potential **donor lymphocytes**.



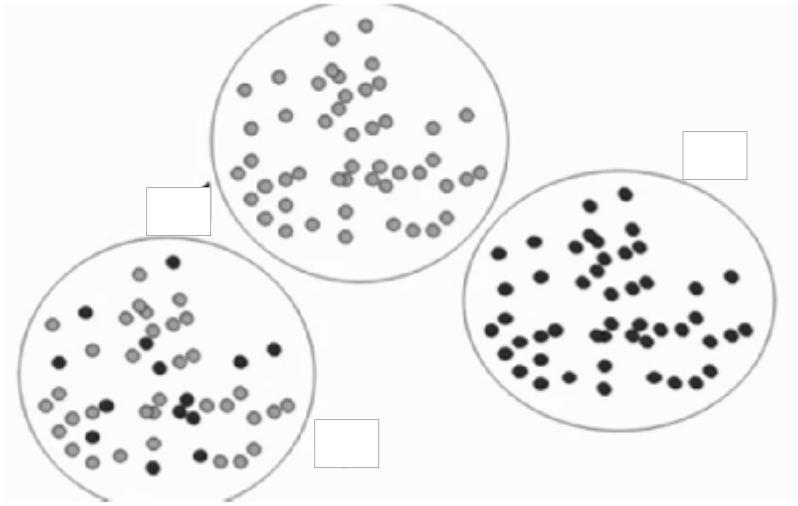


standard CDC detects HLA and non HLA-specific complement fixing antibodies of IgG/IgM classes.

CDC technique



CDC under microscope



Types and mechanisms of graft Rejection

- Hyperacute Rejection
- Acute Rejection
- Chronic Rejection

Hyperacute rejection

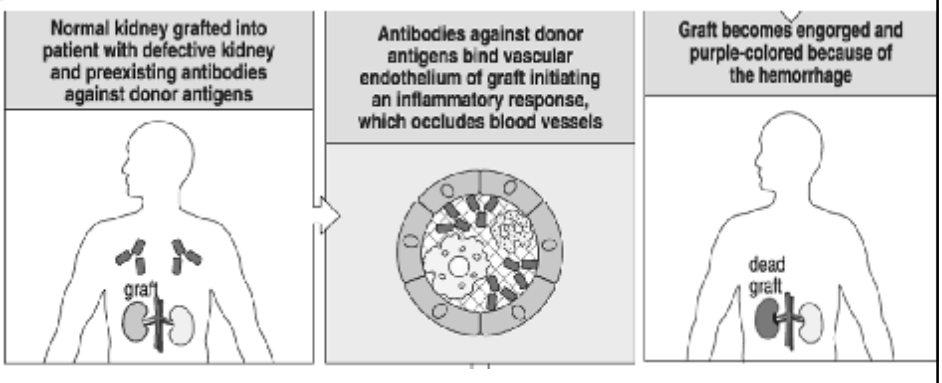
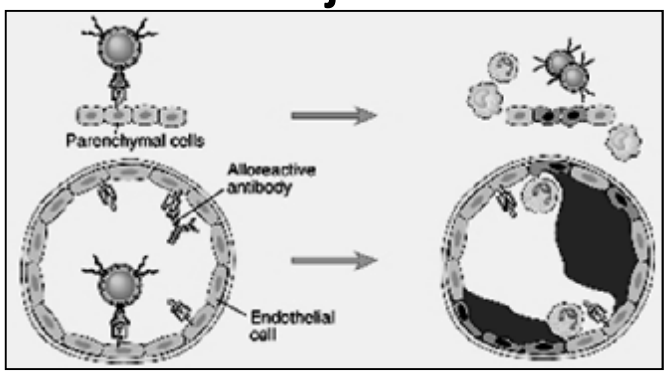


Fig 14-44 immunobiology 7ed. (Garland Science2008)

Acute Rejection



Vascular and parenchymal injury mediated by Alloreactive T cells and antibodies

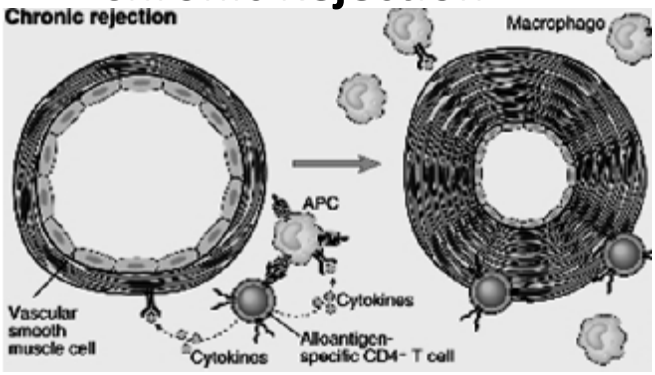
begin after the first week of transplantation

CTLs destroy the graft by cytokines TNF and by perforin- granzyme-mediated killing

Chronic Rejection

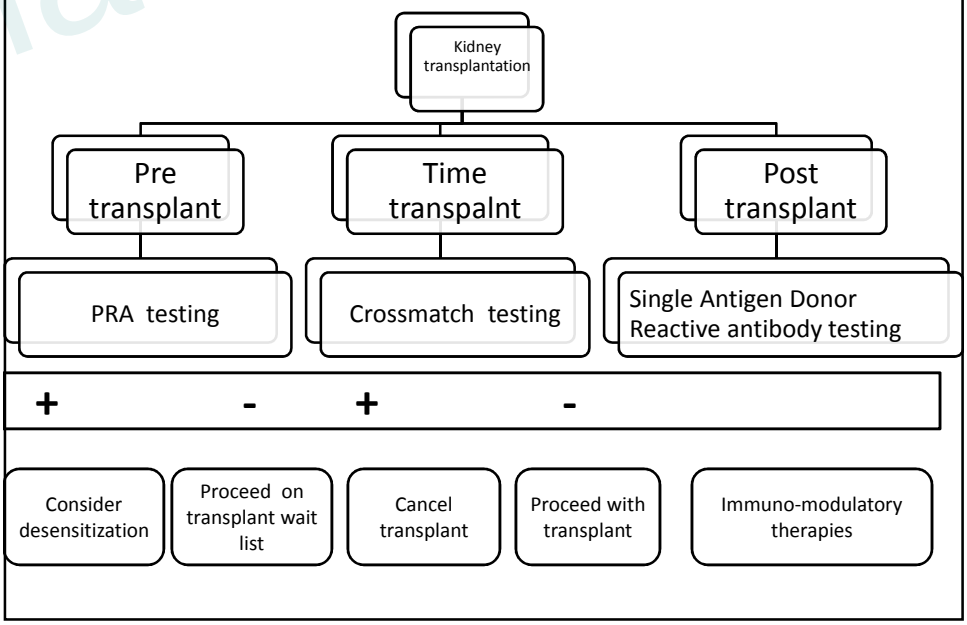
- Occurs in most solid organ transplants several months after transplantation.
- Fibrosis, collagen deposition, and loss of blood flow
- loss of graft function over a prolonged period.
- What triggers CGR is unknown,
  several acute rejection / decreased graft survival.

Chronic Rejection



- Both alloAbs and cell-mediated responses are involved
- cytokines directly damage the grafted tissue
- activated recipient T cells induce mono/MQ that have infiltrated into the graft and endothelial cells in the walls of its blood vessels, to produce growth factors and cytokines

Transplant clinical immunologic testing



Hematopoietic stem cell transplantation

Infuses healthy blood stem cells into the body to replace damaged or diseased stem cells and restore non-functional hematopoietic systems.

Blood stem cells are located in

Bone marrow: most stem cells are found

Peripheral blood: the blood circulating throughout the body

Umbilical cords : newborn babies.

To prepare for a stem cell transplantation

conditioning regimen : high doses of chemotherapy and sometimes radiation therapy.

- Destroy cancer cells and damaged stem cells in patients with diseases such as aplastic anemia.

- Destroy blood-forming cells in the bone marrow to create space for the new, healthy stem cells.

- Suppress IS to prevent rejection of new stem cells.

patients receive infusions of healthy stem cells.

Autologous transplantation,
Allogeneic transplantation

After the stem cells are infused, they travel to the BM, begin the process of forming new, healthy blood cells:

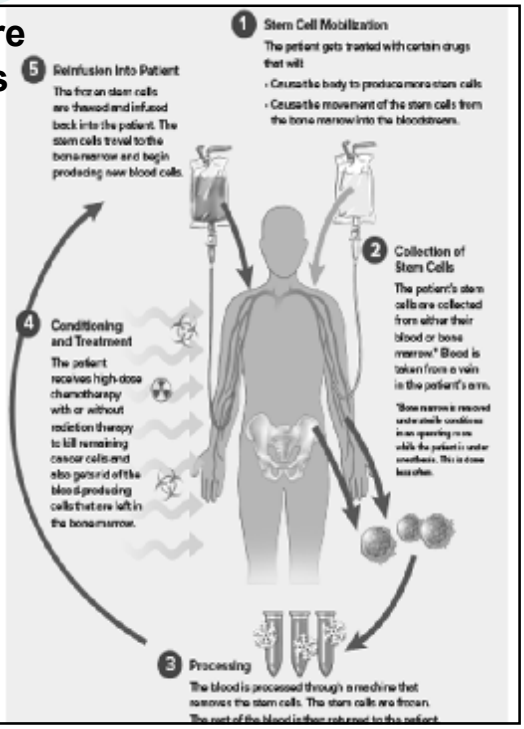
“engraftment.”

Engraftment occurs more quickly in an autologous transplantation

graft failure is rare,

GVHD) is never a problem

No graft-versus-tumor.
a higher risk of relapse of the disease.

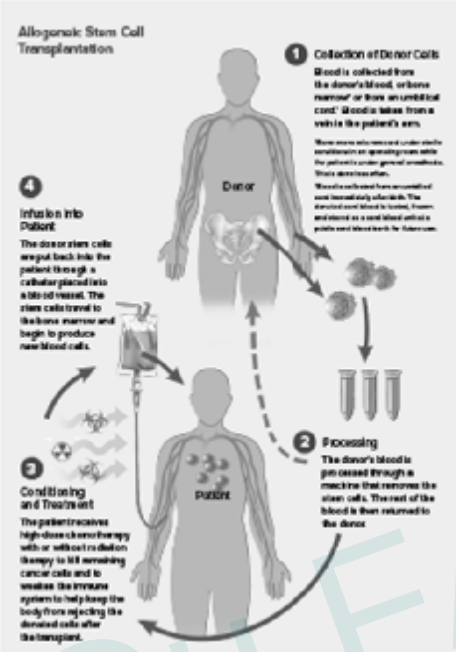


"**graft-versus-tumor effect."** more important than the very intensive conditioning regimen to destroy the cancer cells.

only occur in allogeneic stem cell transplantation.

reject the donated stem cells before they are able to engraft

graft-versus-host disease" (GVHD).



HSC Transplantation

Indications

- **Malignant diseases**
  - Acute and chronic leukemia
  - Lymphoma, nonhodgkin lymphoma,
  - Multiple myeloma
  - Myelodisplasia
  - Aplastic anemia

Bone Marrow Transplantation
Indications

- **Genetic diseases**
  - Severe combined immunodeficiency (SCID)
  - Wiskott – Aldrich syndrome
  - Chronic granulomatous disease
  - Chédiak- Higashi syndrome
  - Ataxia telanglectasia
  - Mucopolysaccharidosis
  - Gaucher's disease
  - Thalassemia major, sickle cell anemia
  - Fanconi's anemia
  - Osteopetrosis

Donor Limitations

25 – 30% of patients have an HLA-identical sibling

- Autologous transplantation (marrow procured during remession)
- related HLA-identical/ non –identical living donors
- unrelated living donors

Bone Marrow Transplantation
Complications

- Graft Rejection
- Graft-vs-host disease (GVHD)
- Infections
- Prolonged immunodeficiency
- Disease recurrence

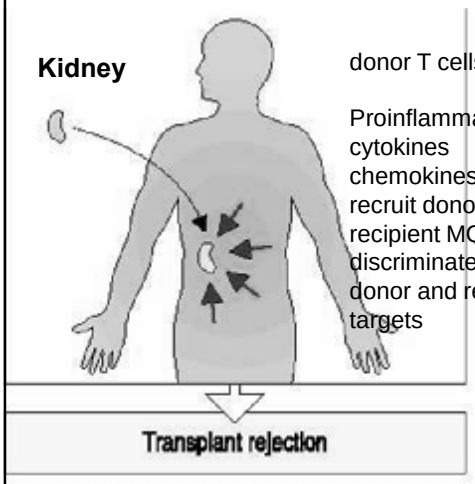
Graft Rejection

the immunologic rejection of donor hematopoietic elements by **the residual host immune system.**

Graft rejection occurs
- patients receiving unrelated or mismatched transplants

- reduced-intensity regimens, especially in patients who are not pretreated heavily.

GvHD : systemic disease



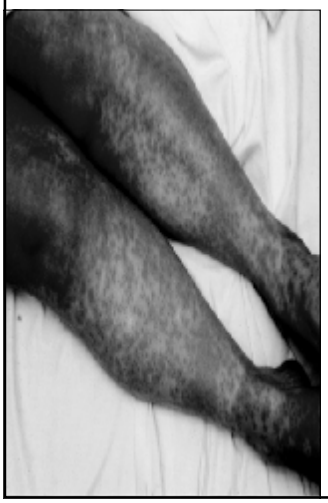
donor T cells

Proinflammatory cytokines chemokines recruit donor and recipient MQ, NK not discriminate between donor and recipient targets

Stem Cell Transplantation

Graft-versus-host disease

cont. *Symptoms and signs*



Fever
Exfoliative dermatitis
Hepatitis/ hyperbilirubinemia
Vomiting, diarrhea
Abdominal pain
Weight loss

Occurrence of GvHD

- Acute GvHD: 75% of HCT recipients with a mismatch at a single MHC locus, and in 80% of recipients with three mismatches.
- Disparities in MHC class II alleles are at higher risk for developing GvHD than are those with mismatched MHC class I alleles.
- Even among recipients completely matched at all MHC loci, about 30–50% will develop clinically significant GvHD due to MiHA mismatches.

Graft vs. Host Disease

- **Acute GvHD**
  - Characterized by epithelial cell death in the skin, GI tract, and liver
- **Chronic GvHD**
  - Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs

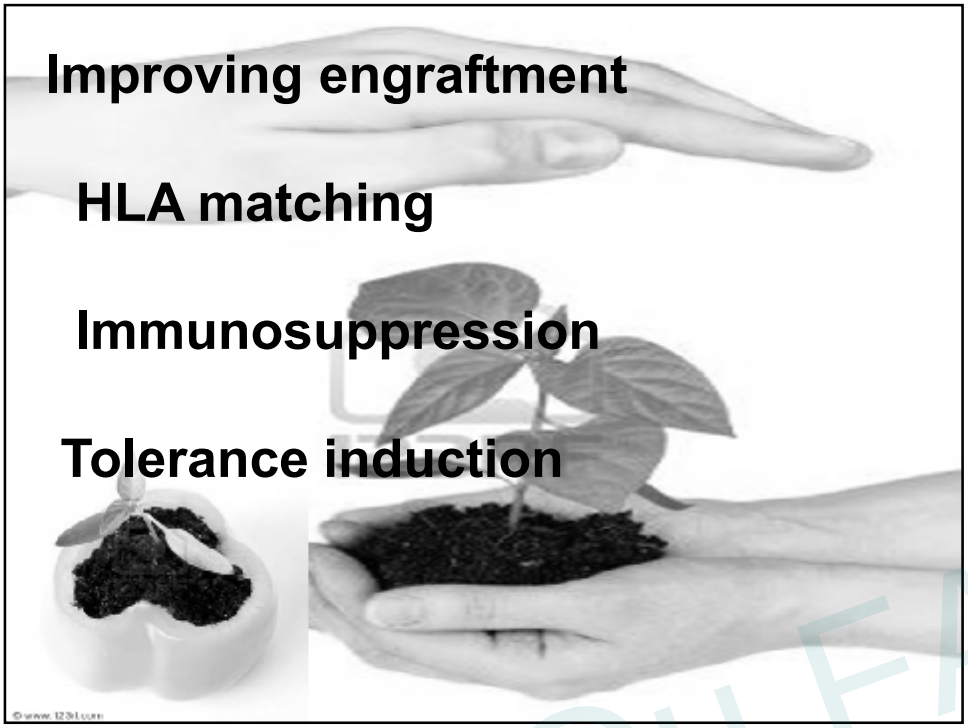
Graft vs. Host Disease

The more closely matched the donor and recipient are, the less risk of potentially life-threatening graft-versus-host disease (GvHD)

- Occurrence of GvHD presents problems, but has been linked to a decrease in relapse risk

Graft-versus-leukemia (GVL) effect

Donor T cells are eliminated ⇨ relapse



Immunosuppressive drugs

– **Corticosteroids** such as prednisolone suppress the inflammation associated with transplant rejection

– **Azathioprines** disrupt the synthesis of DNA and RNA and cell division.

– **Cyclosporins** act by inhibiting T-cell activation, thus preventing T-cells from attacking the transplanted organ.

Immunosuppressive drugs

Corticosteroids

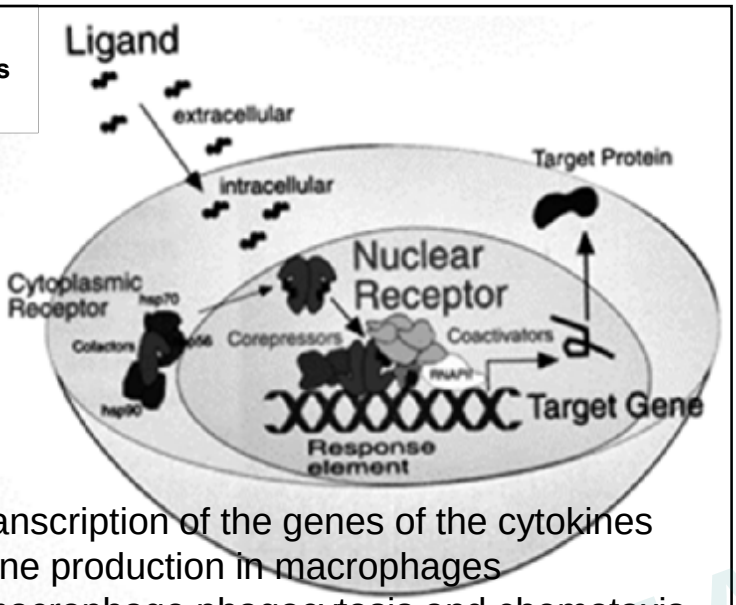
(Prednisone , Methylprednisolone)

•non-specific

• Used in maintenance immunosupp°/ treatment AR

• Block T cell and APC derived cytokine and cytokine-R expression (IL-1,IL-6, IL-2,INF-γ ,TNF-α) .

Corticosteroids



- •inhibit the transcription of the genes of the cytokines
- •inhibit cytokine production in macrophages
- • Inhibit the macrophage phagocytosis and chemotaxis properties.
- • Acute reduction of circulating lymphocytes and MO.

Side Effects Associated with Immunosuppressants:

alopecia - loss of hair, baldness

anemia - a pathological deficiency in the oxygen carrying compound of the blood

arthralgias - pain experienced in the joints

bone marrow depletion - a depletion of bone marrow (a soft, fatty, vascular tissue that fills most bone cavities - it is the source of blood cells)

coronary artery disease - a stage of arteriosclerosis involving fatty deposits inside the artery walls that feed the heart

cushingoid appearance - moon face, buffalo hump, centripetal obesity

gastrointestinal upsets - discomfort spurring from the stomach and/or intestines

gingival hyperplasia - an increase in the amount of gum tissue in the mouth

glaucoma - eye diseases characterized by high intraocular fluid pressure, damaged optic disk, hardening of the eyeball, and loss of vision

hepatoxicity - damage to the liver

hirsutism - excess facial and body hair

hypercholesterolemia - the presence of excess cholesterol in blood

hyperglycemia - the presence of excess sugar in the blood

hyperkalemia - a condition where potassium levels are too high in the body

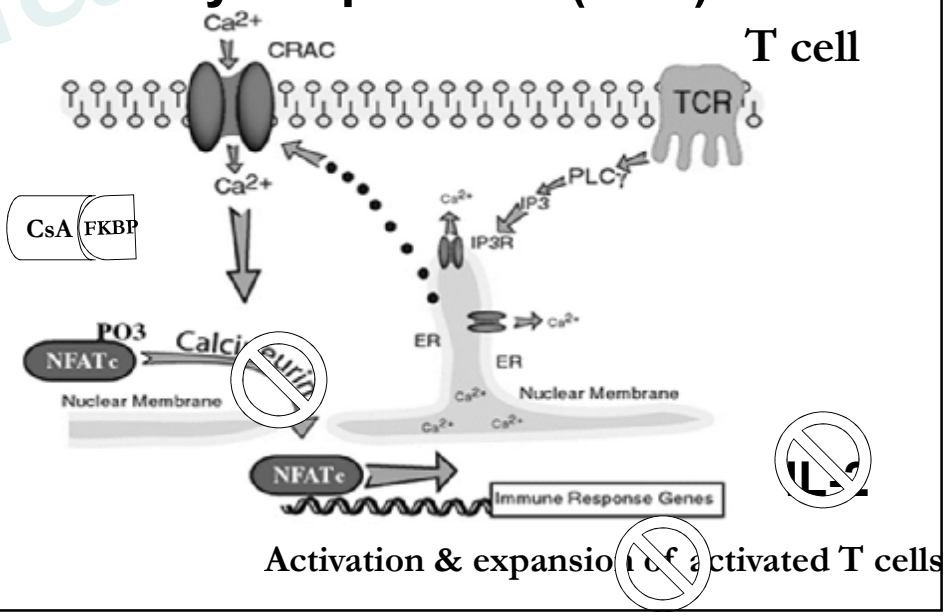
hyperlipidemia - the presence of excess fat or lipids in the blood

hypertension - abnormally high blood pressure - especially arterial blood pressure

Azathioprine

- Rapidly hydrolyzed in the blood to 6-mercaptopurine.
- Incorporates into the DNA,
- Inhibiting nucleotide synthesis.
- Prevents mitosis and proliferation of rapidly dividing cells (activated B and T lymphocytes)
- Excessive suppression, bone marrow aplasia can result, Hepatotoxicity

Cyclosporine A (CsA)



Activation & expansion of activated T cells

Mycophenolate Mofetil

• Blocks T and B proliferation by inhibiting the inosine monophosphate dehydrogenase (purine synthesis)

• DNA replication is blocked, lymphocytes cannot proliferate

• Decreases the risk (by more than 50%) of acute rejection episodes within the first year of transplantation,

• Decreases significantly CGR.

• MMF is not diabetogenic, neurotoxic, or nephrotoxic,

• Nausea, vomiting, diarrhea, leucopenia, and thrombocytopenia

Polyclonal Antibodies

• Polyclonal Antibodies are used in prophylaxis or treatment of rejection

• Directed against lymphocyte antigens (multiple epitopes).

• Derived from either horses or rabbits.

• Antibodies specific for many common T cell surface antigens including CD2, CD3,CD4, CD8, CD11a, CD18.

• Depletion of T-cell through complement-dependent cytolysis and cell mediated opsonization

Monoclonal Antibodies

• Prophylaxis and treatment of rejection.

• Suppress the activity of subpopulation of T-cells

• Depletion of T cells from the circulation by binding of antibody coated T cells to Fc receptors on phagocytic cells.

•Block co-stimulatory signals

•Ab specific for implicated cytokine can prolong the survival of graft.

•Treat donor's bone marrow before it is transplanted

Side Effects

Laboratories routinely use murine antibodies as a starting point for monoclonal antibodies

•Human anti-murine Antibody response

eliminate murine Abs from circulation. Ineffective monoclonal therapy

• serum sickness

counteractive measure humanizing (chimerizing) Abs

Splice and replace the constant region of the murine antibody with that of a characteristic human antibody

more effective

less adverse side effects.

Basiliximab (70% human and 30% murine)
Daclizumab i(90% human and 10% murine).

- Used in the prevention of acute organ rejection.
- Specific,high affinity (IL-2Rα)
- prevent IL-2 from binding to the receptor on the surface of activated T cells.
- Inhibit activation and proliferation of T cells.
- A long half-life of (7-12 days) and saturates the IL-2 receptor for up to 59 days.

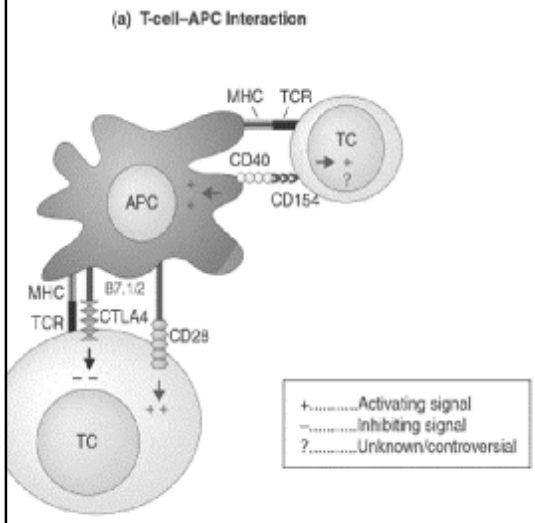
Improving engraftment

HLA matching

Immunosuppression

Tolerance induction

Blocking co-stimulation through CD28 or CD40



Ethical aspects

- Declaring patients dead before they are completely dead?
- compensation for organ donation?
- Organs for sale !?