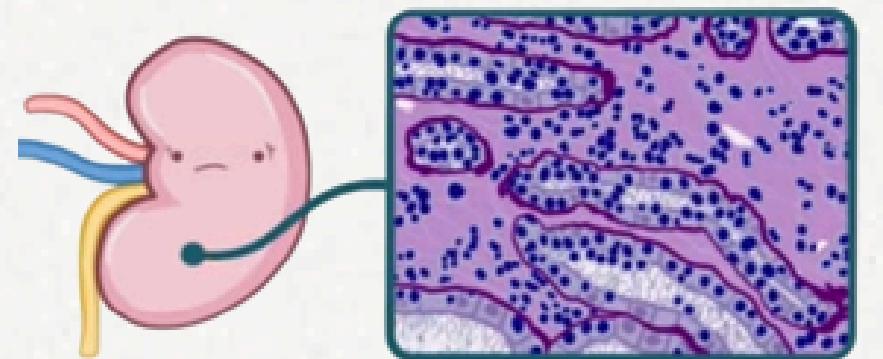


IMMUNE RESPONSE RELATED TO ORGAN TRANSPLANT AND GRAFT REJECTION



01 | CASE STUDY

RAMESH - 50 YR OLD



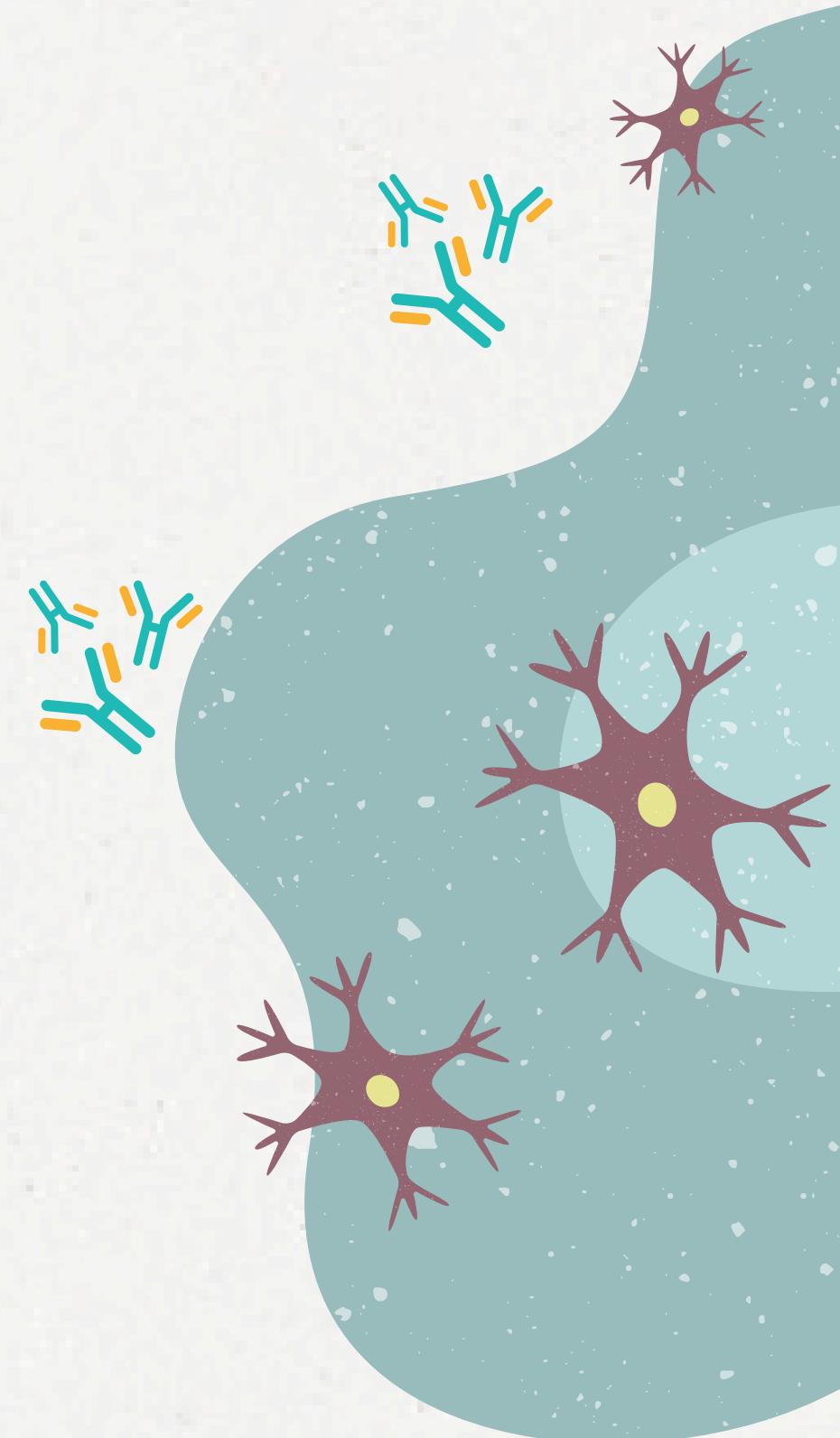
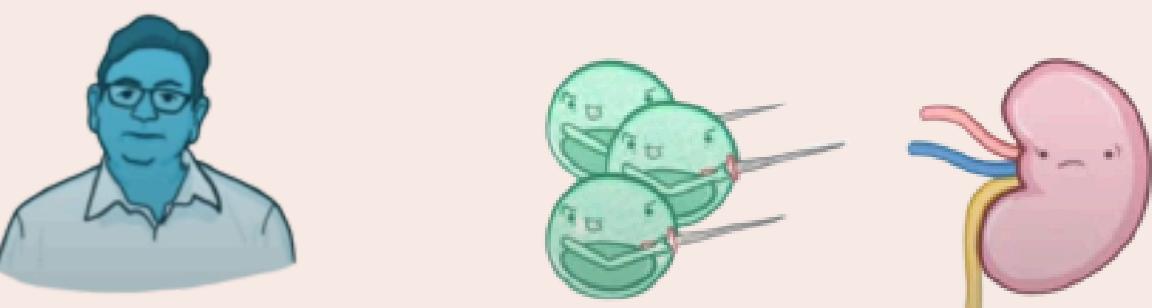
- FEVER
- ↓ PRODUCTION OF URINE
- KIDNEY TRANSPLANTATION ONE MONTH AGO
- HIGH BP



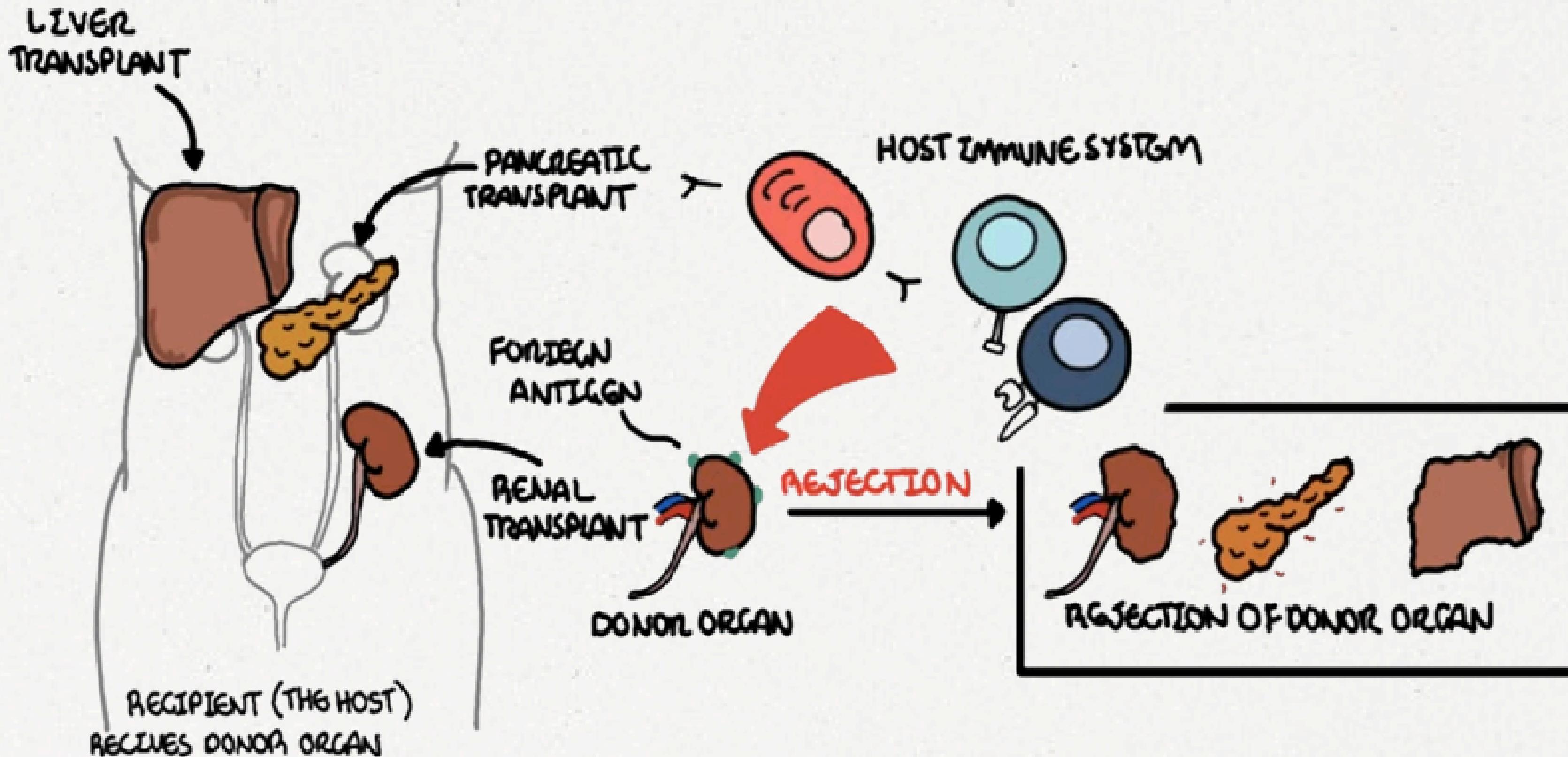
- * BIOPSY
 - └ DENSE LYMPHOCYTIC INFILTRATE i.e presence of plasma cells

CONCLUSION

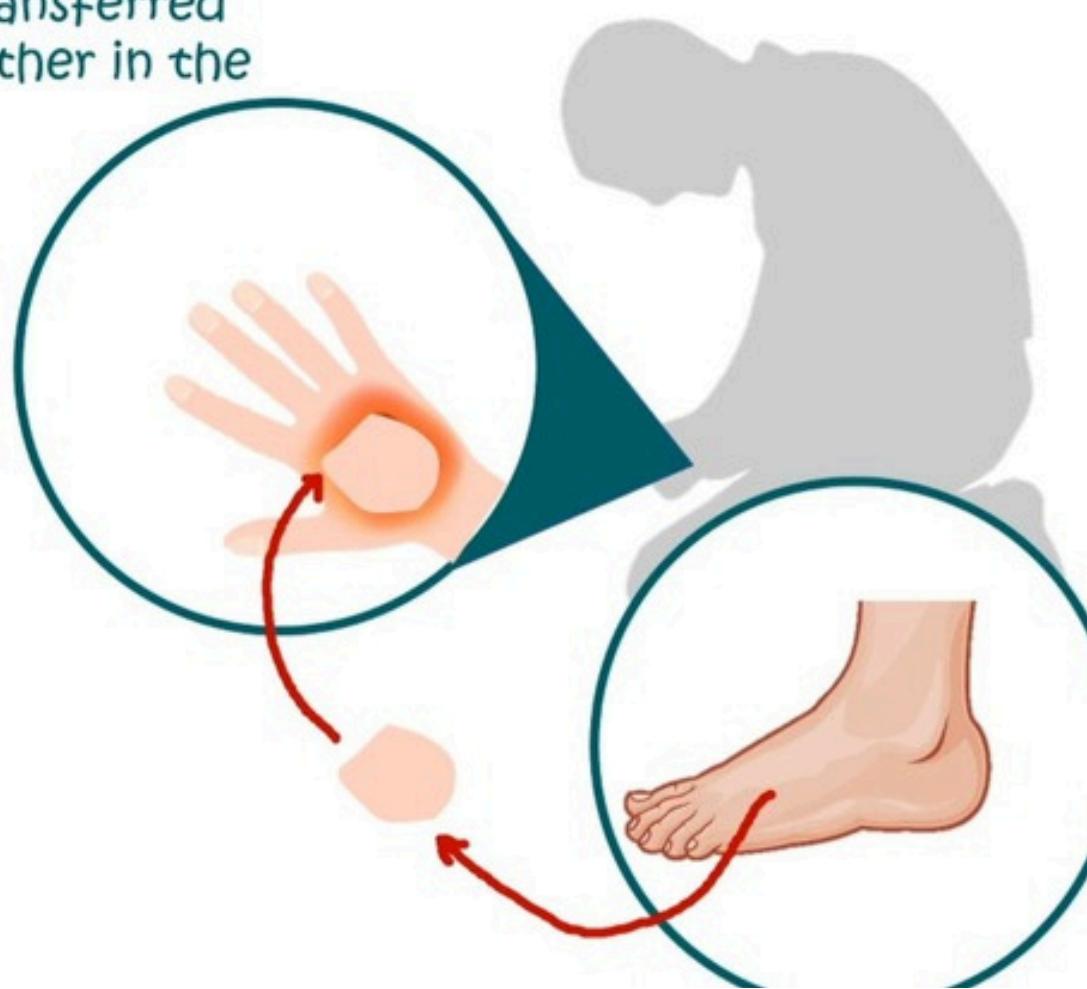
RAMESH ORGAN TRANSPLANT REJECTION



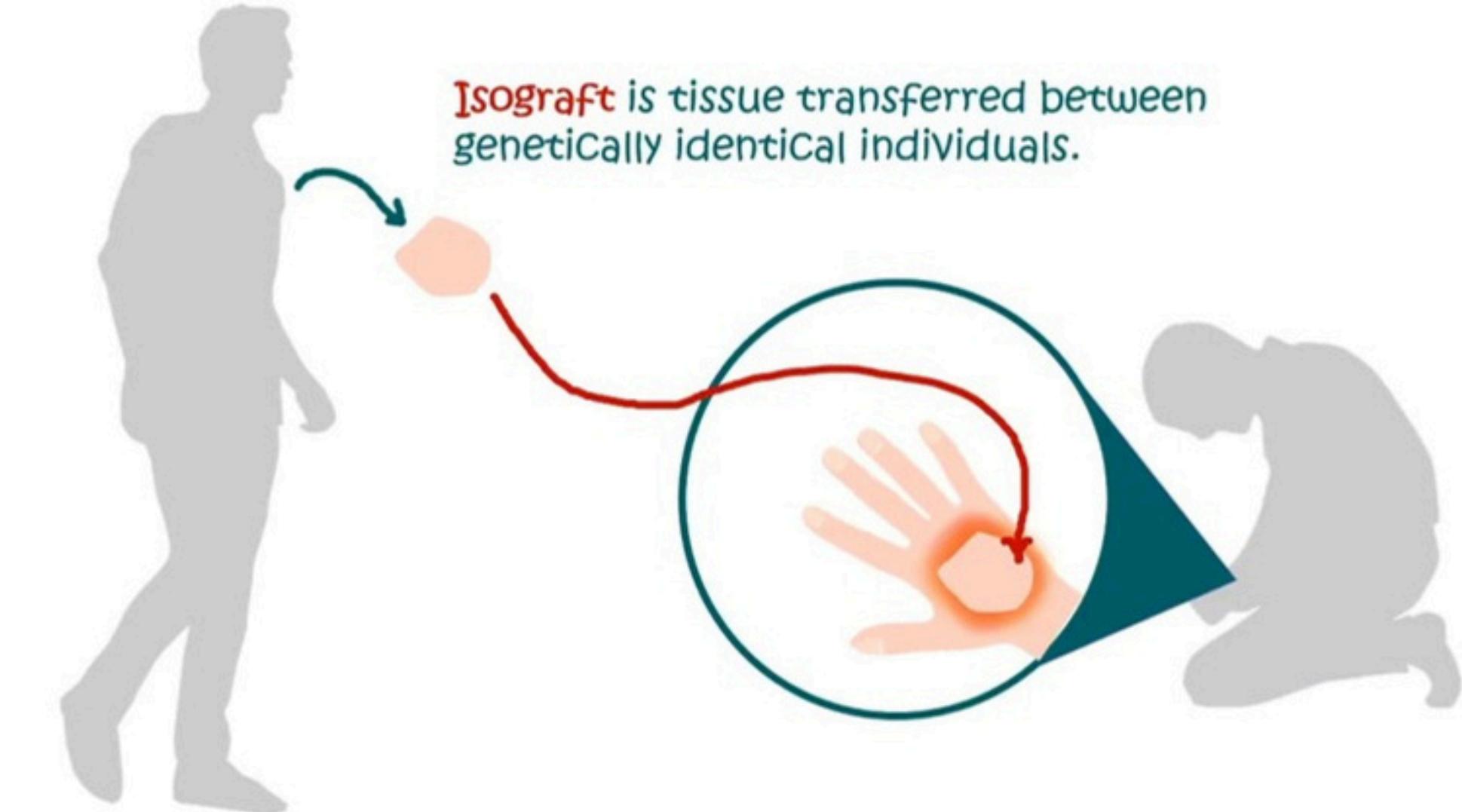
02 | WHAT IS TRANSPLANT REJECTION ?



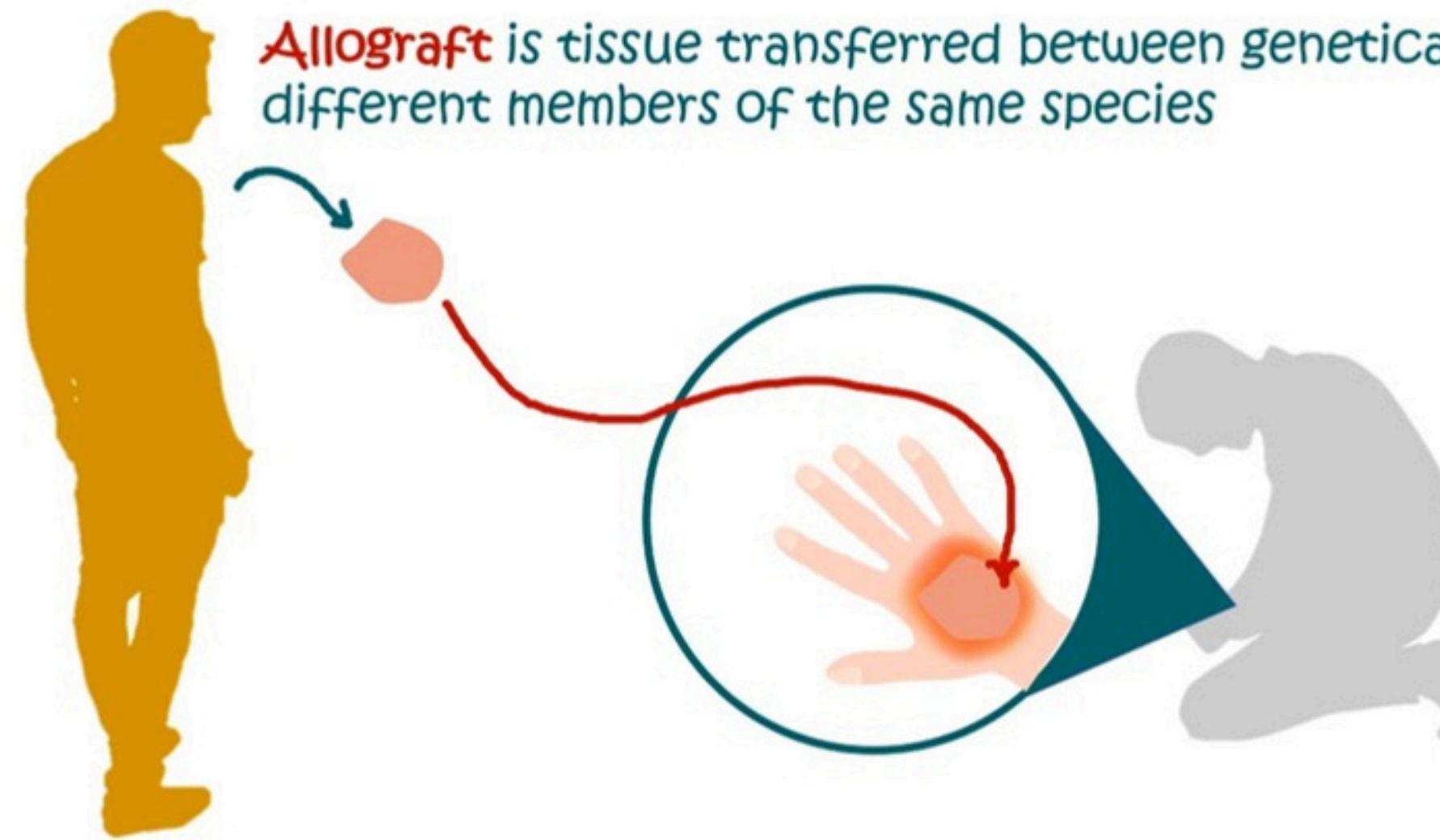
Autograft is self-tissue transferred from one body site to another in the same individual.



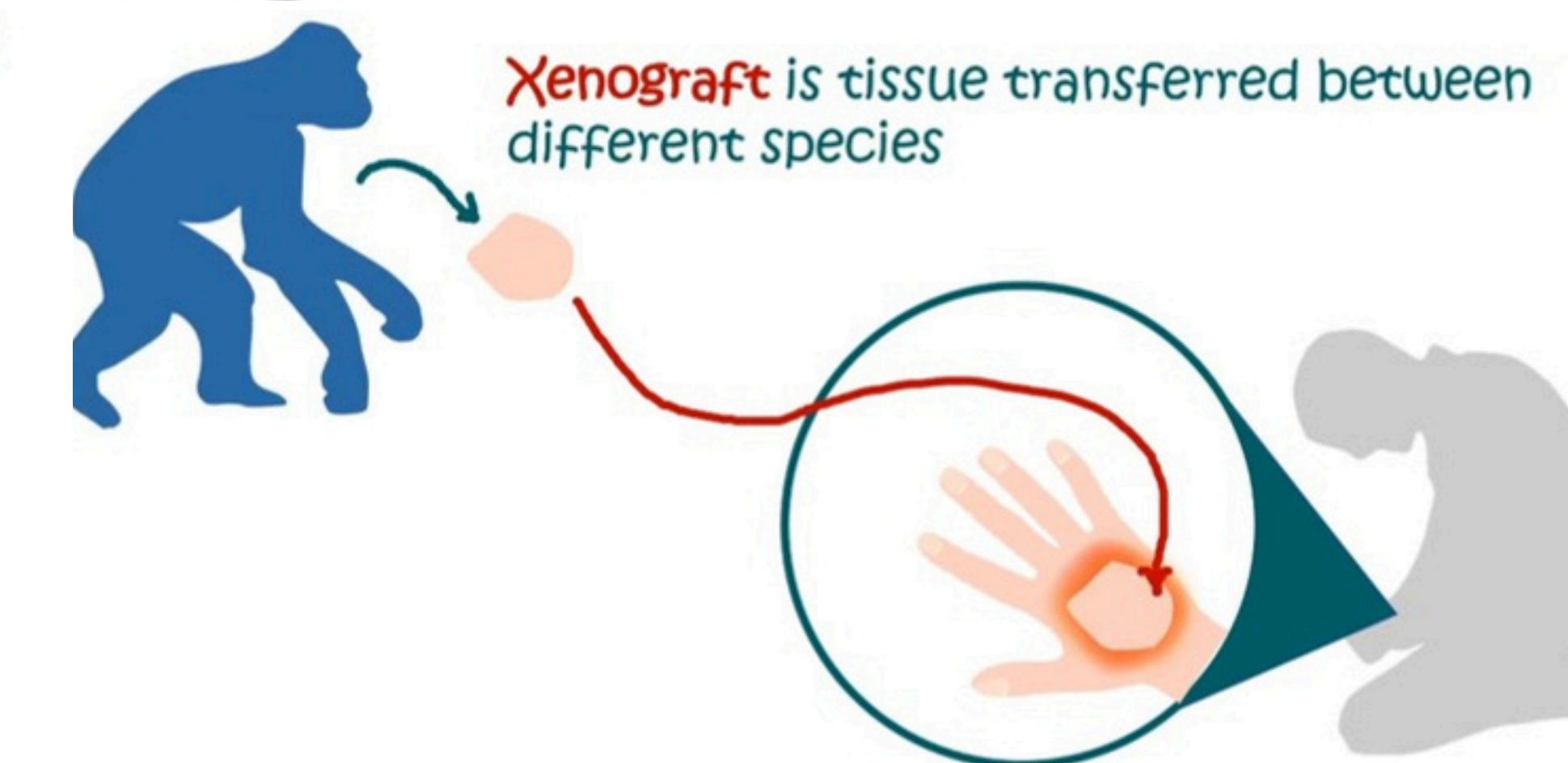
Isograft is tissue transferred between genetically identical individuals.



Allograft is tissue transferred between genetically different members of the same species



Xenograft is tissue transferred between different species

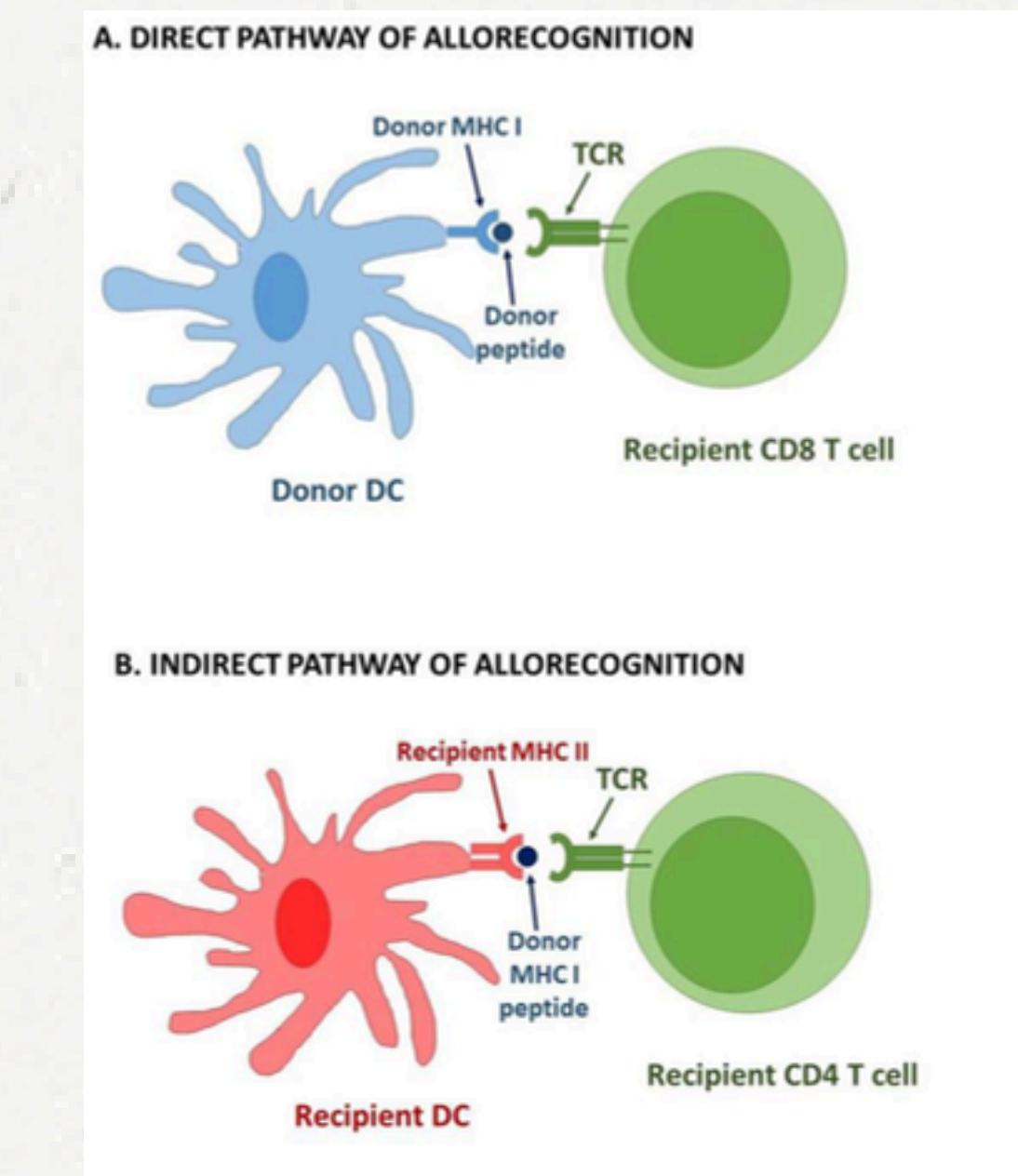
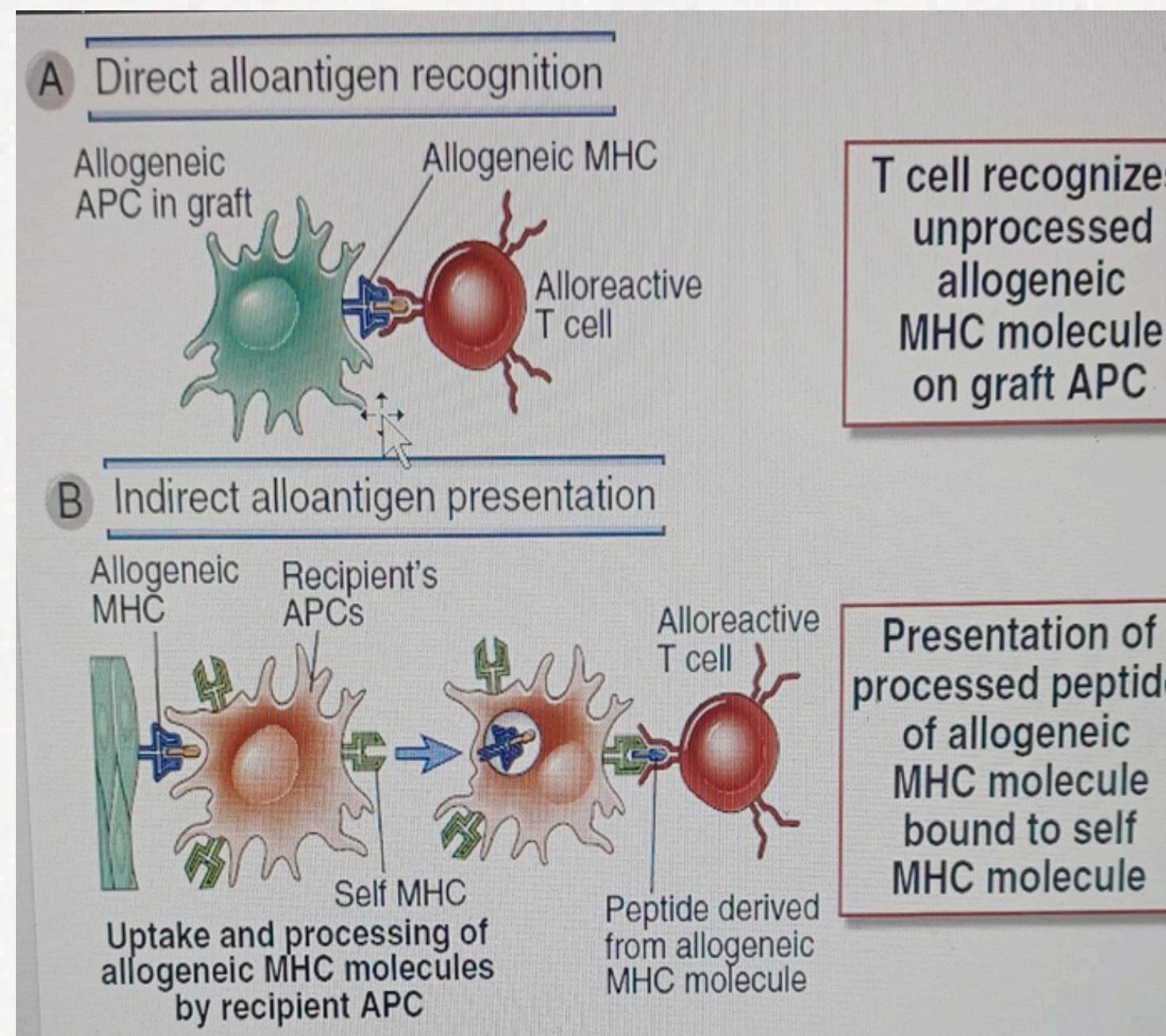


07 | GRAFT REJECTION

- Graft rejection happens when the host's immune system attacks the donated graft and starts to destroy the transplanted tissue/organ.
- There are 2 mechanisms of rejection:-
 1. Cell Mediated Rejection
 2. Antibody Mediated Rejection

08 | DIRECT VS INDIRECT PATHWAY

- **Direct** - Grafted cells directly present the unprocessed antigens to T cells.
- **Indirect** - Grafted cells first present the antigens to recipient APCs, which process the antigens. Then the host APCs will present the processed antigen to T cells.

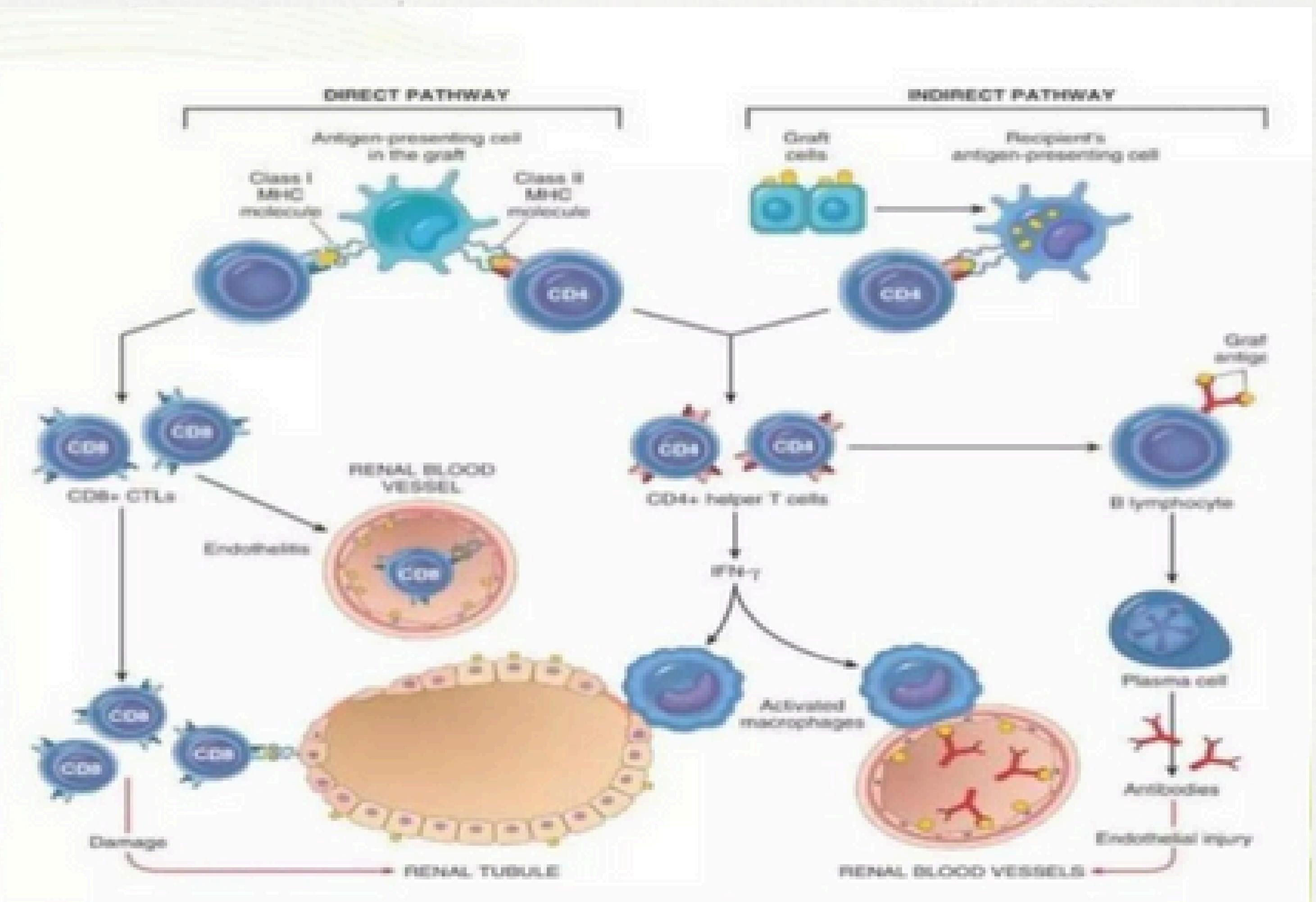


09 | CELL MEDIATED REJECTION MECHANISM

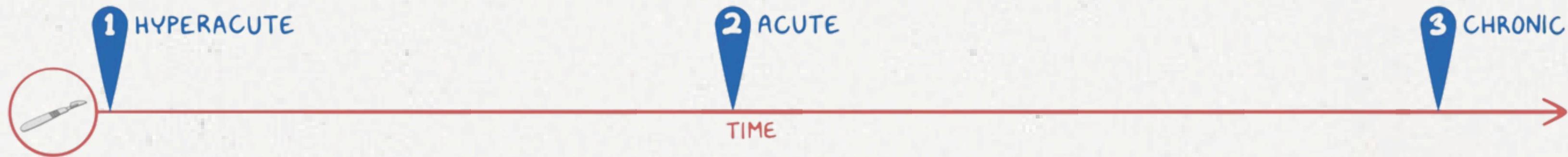
- Activation of T cells:- Recipient T cells activate after encountering donor antigens.
- Infiltration of T cells:- Activated T cells migrate to the transplanted organ and infiltrate the tissue.
- T cell recognition of donor antigen:- Activated T cells recognize and bind to the donor antigens.
- Release of Cytokines and Cytotoxic Chemicals:- Cytokines such as interferons-gamma is released that activates the other immune cells such as macrophages to attack the organ.
- Tissue damage and Rejection:- They will kill the cells that contain the foreign antigen which will lead to inflammation in the endothelium, thrombosis and graft ischemia.

10 | ANTIBODY MEDIATED REJECTION MECHANISM

- Formation of DSAs:- Recipients Immune system recognizes donor antigens and produces antibodies against them. They are specific to donor antigens.
- Binding of Ab to donor antigen:- DSAs bind to the donor antigens.
- Activation of complement system:- complement system is a group of proteins that damage the tissue. An activated protein (C5a) helps to form the Membrane Attack Complex. This MAC causes cell lysis and ultimately cell injury.
- Recruitment of immune cells:- One of the activated proteins (C3a) stimulates monocytes, macrophages and neutrophils. These immune cells release cytokines which further recruits NK cells.
- Tissue damage and Rejection:- Cell injury leads to platelets aggregation which results in thrombosis and graft ischemia



03 | TYPES



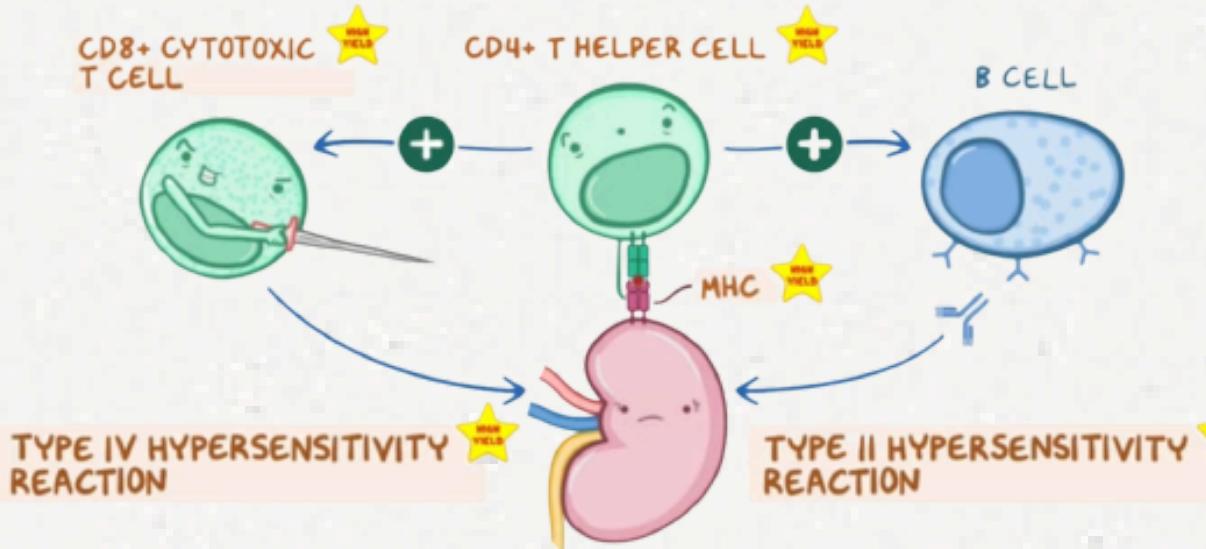
- Starts within minutes
- Type II Hypersensitive reaction
- i.e. the recipient's blood has preformed antibodies bound to the Transplanted organ\ Graft



TREATMENT:

PROMPT GRAFT REMOVAL

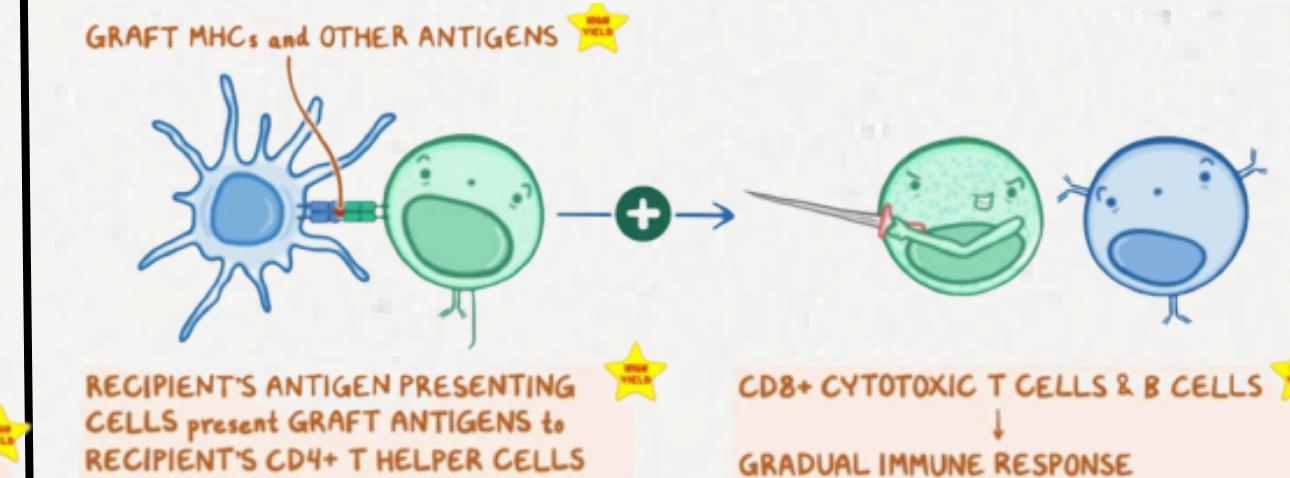
- Weeks / months after transplant
- Takes longer to develop since there are no preformed antibodies



TREATMENT:

IMMUNOSUPPRESSIVE THERAPY

- Months / years after transplant
- Type IV and type II Hypersensitive reaction

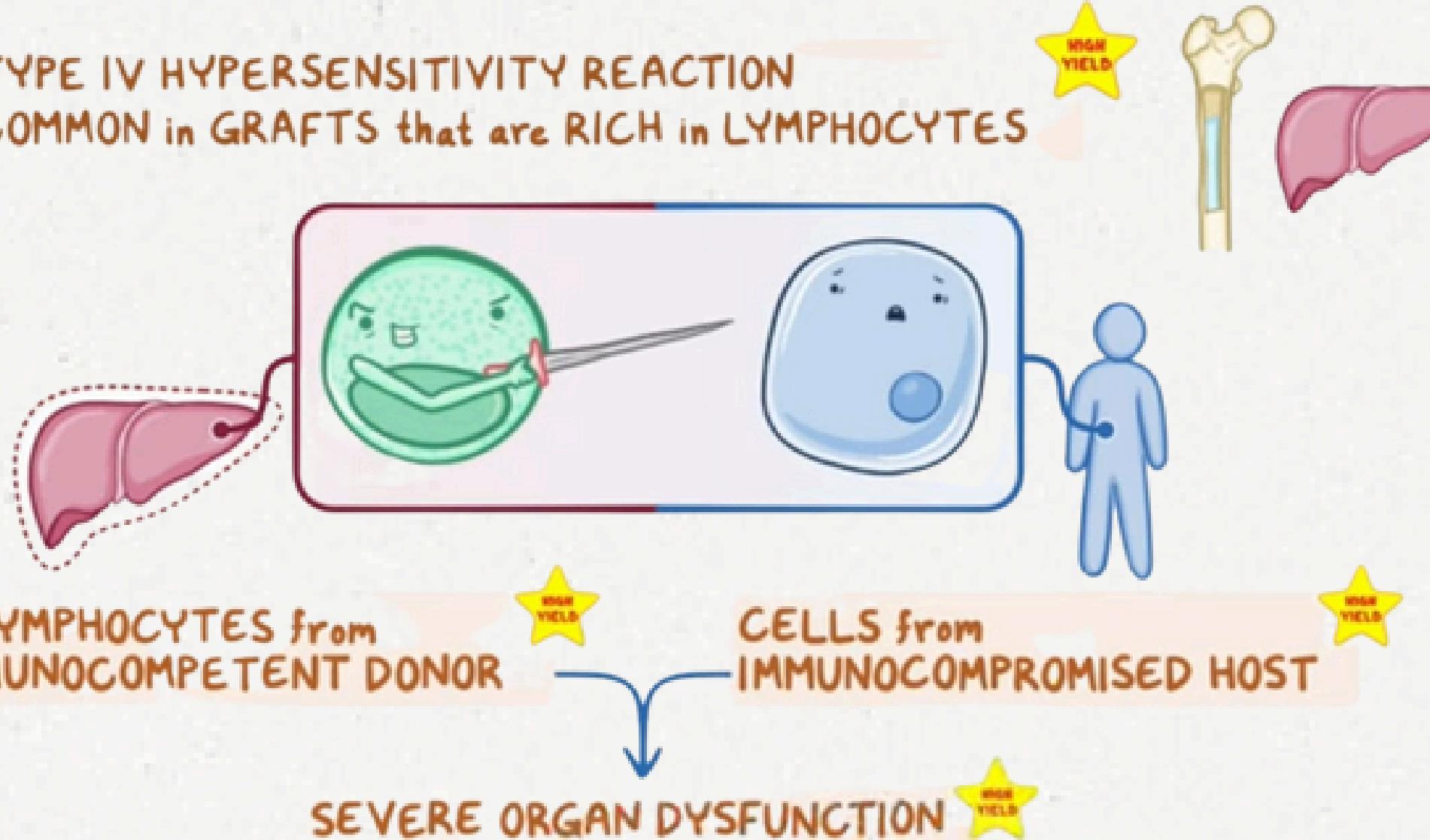


TREATMENT:

CAN'T BE PREVENTED / TREATED

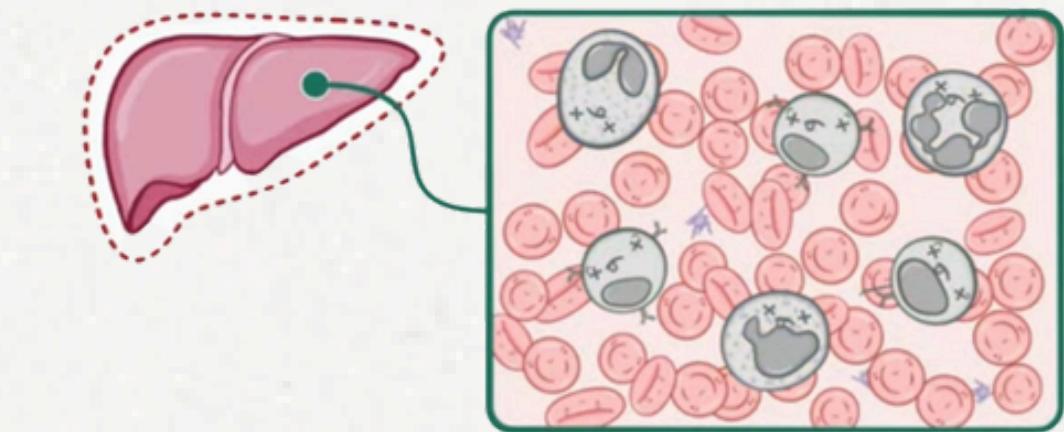
04 | GRAFT VS HOST DISEASE (GvHD)

- * TYPE IV HYPERSENSITIVITY REACTION
- * COMMON in GRAFTS that are RICH in LYMPHOCYTES



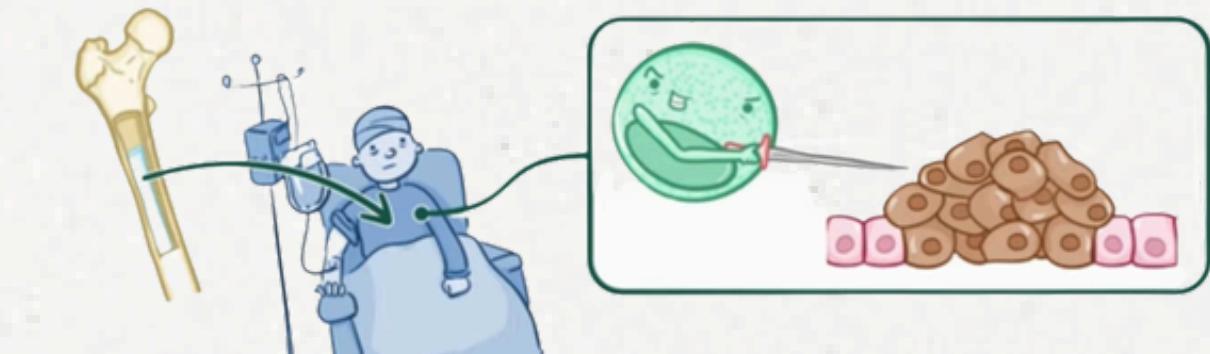
PREVENTION :

IRRADIATING BLOOD PRODUCTS to KILL the LYMPHOCYTES PRIOR to TRANSFUSION



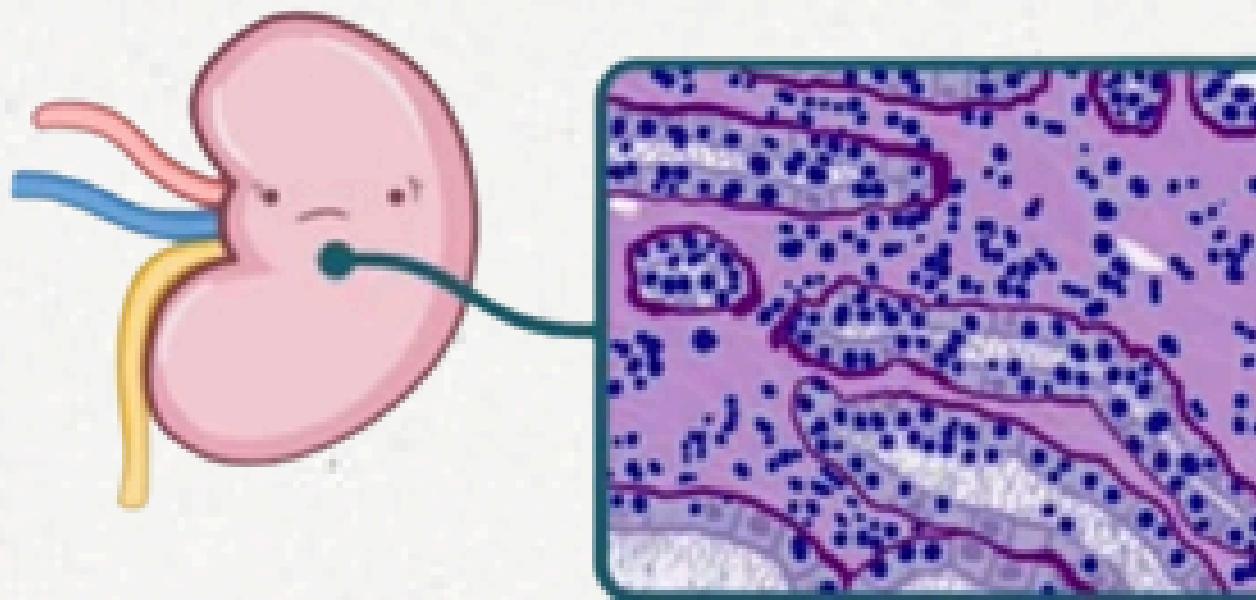
GRAFT VS TUMOR EFFECT

Situations where GvHD is Induced on purpose in individuals who have leukemia



05 | CONCLUSION OF CASE STUDY

RAMESH - 50 YR OLD



- * FEVER
- * MALAISE
- * OLIGURIA
- * HYPERTENSION
- * KIDNEY TRANSPLANT ONE MONTH AGO

ACUTE TRANSPLANT REJECTION

CONFIRMED with BIOPSY
└ DENSE LYMPHOCYTIC INFILTRATE

Minimizing rejection

ABO blood group compatibility

Compatibility Of Blood Types								
Recipient	Donor							
	O-	O+	B-	B+	A-	A+	AB-	AB+
AB+	✓	✓	✓	✓	✓	✓	✓	✓
AB-	✓	X	✓	X	✓	X	✓	X
A+	✓	✓	X	X	✓	✓	X	X
A-	✓	X	X	X	✓	X	X	X
B+	✓	✓	✓	✓	X	X	X	X
B-	✓	X	✓	X	X	X	X	X
O+	✓	✓	X	X	X	X	X	X
O-	✓	X	X	X	X	X	X	X

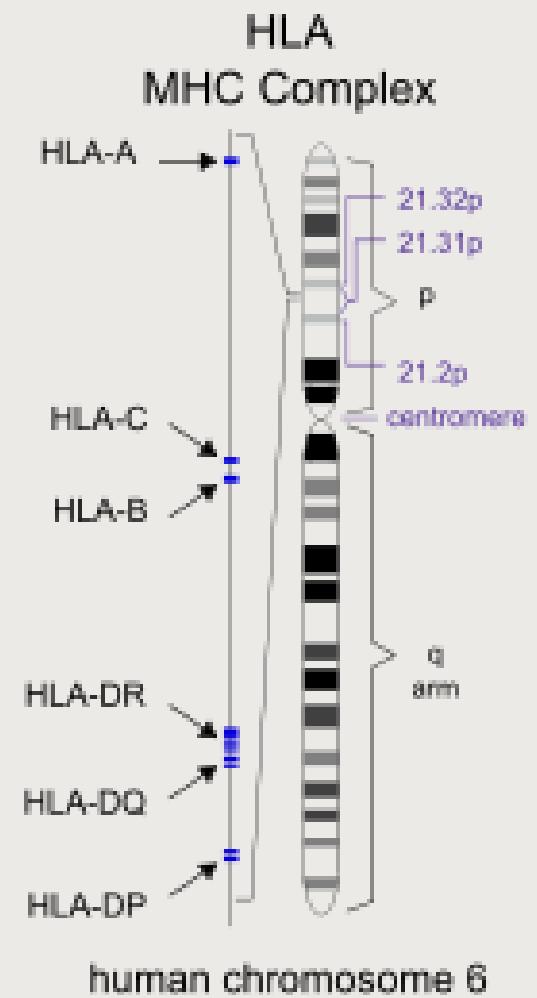
Donor-recipient blood compatibility chart (reproduced with permission) © Héma-Québec, 1998.

This is the first test to be carried out as the transplant will be rapidly rejected if the blood groups do no match

Tissue typing

Helps to find histone compatible between the donor and the recipient.

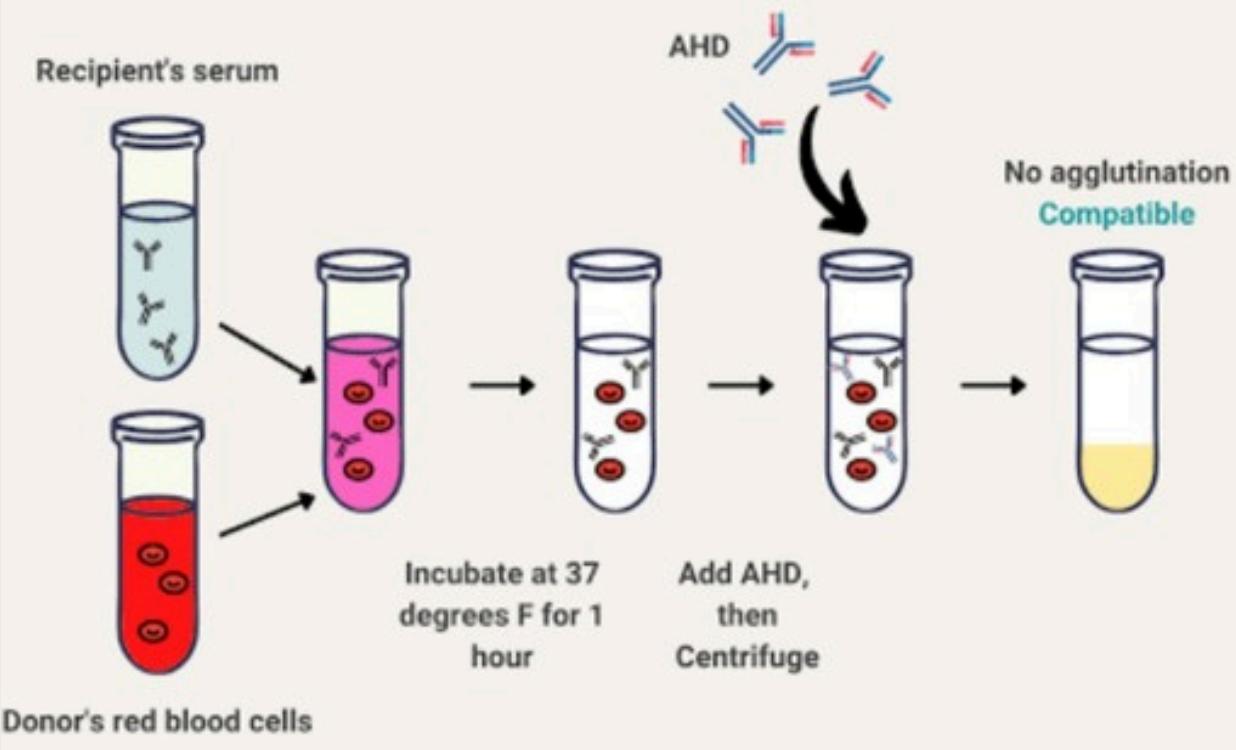
The more alike the HLA types of the donor and recipient are the more likely a transplant will be successful.



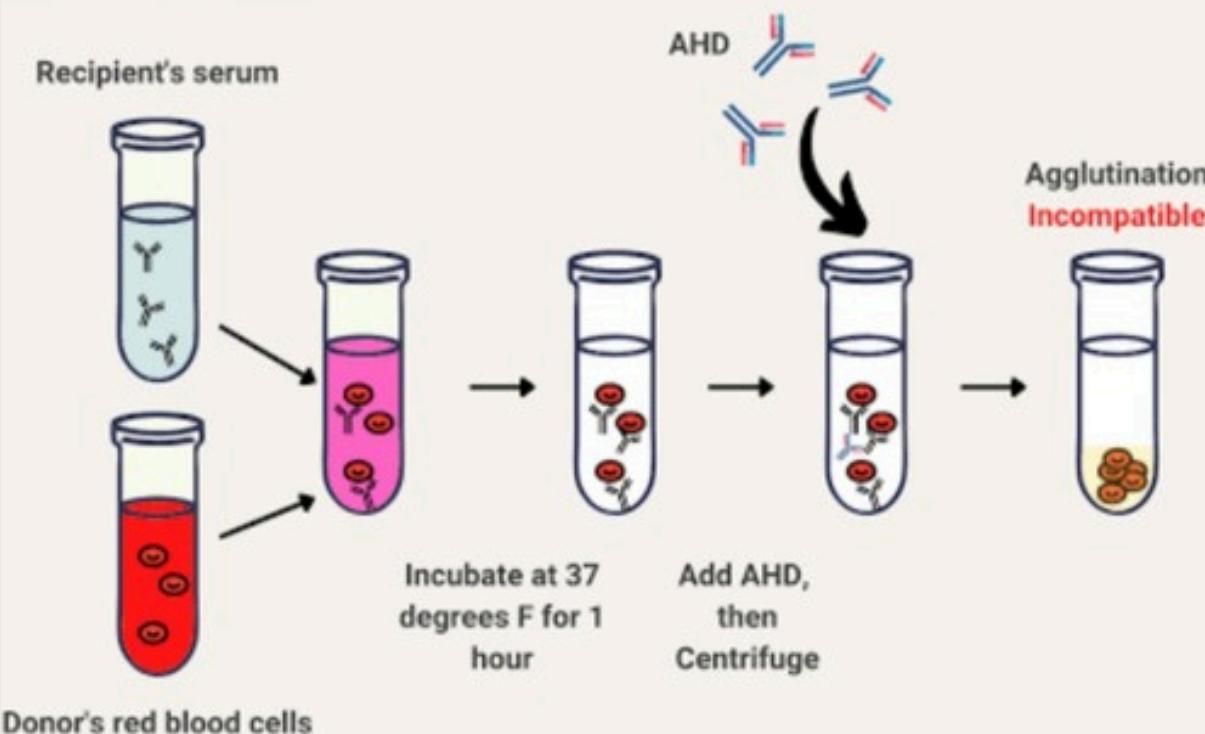
Cross matching

Crossmatch

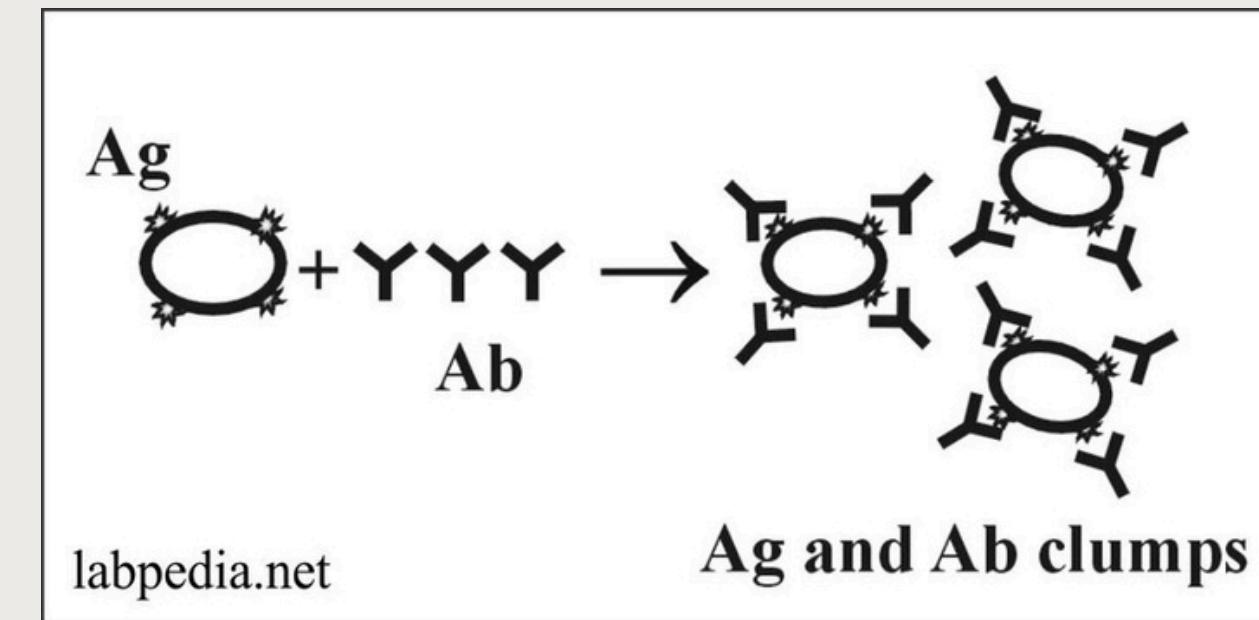
Compatible



Incompatible



Serology test



This is undertaken to detect the immune status of both the donor and a potential recipient against a number of clinically significant infectious organisms, including viruses like HIV, etc.

06 | IMMUNOSUPPRESSANTS

WHAT ARE IMMUNOSUPPRESSANTS?

- Substances/Medications that dial down the immune system's response to the donor organ or graft tissues.
- Immunosuppressants are used to prevent the immune system from attacking the transplanted organ or tissue, thus reducing the risk of rejection.
- They are of several types, namely: -
 1. Calcineurin inhibitors- cyclosporine, tacrolimus
 2. Corticosteroids- prednisone, dexamethasone, hydrocortisone
 3. Antimetabolites- mycophenolate mofetil, azathioprine

WHY DO WE NEED THEM?

- The immune system is responsible for protecting the body by identifying and destroying foreign substances. This backfires when the system recognizes the transplanted organ or tissue as foreign and mounts an immune response against it.
- So, immunosuppressants!



06 | IMMUNOSUPPRESSANTS

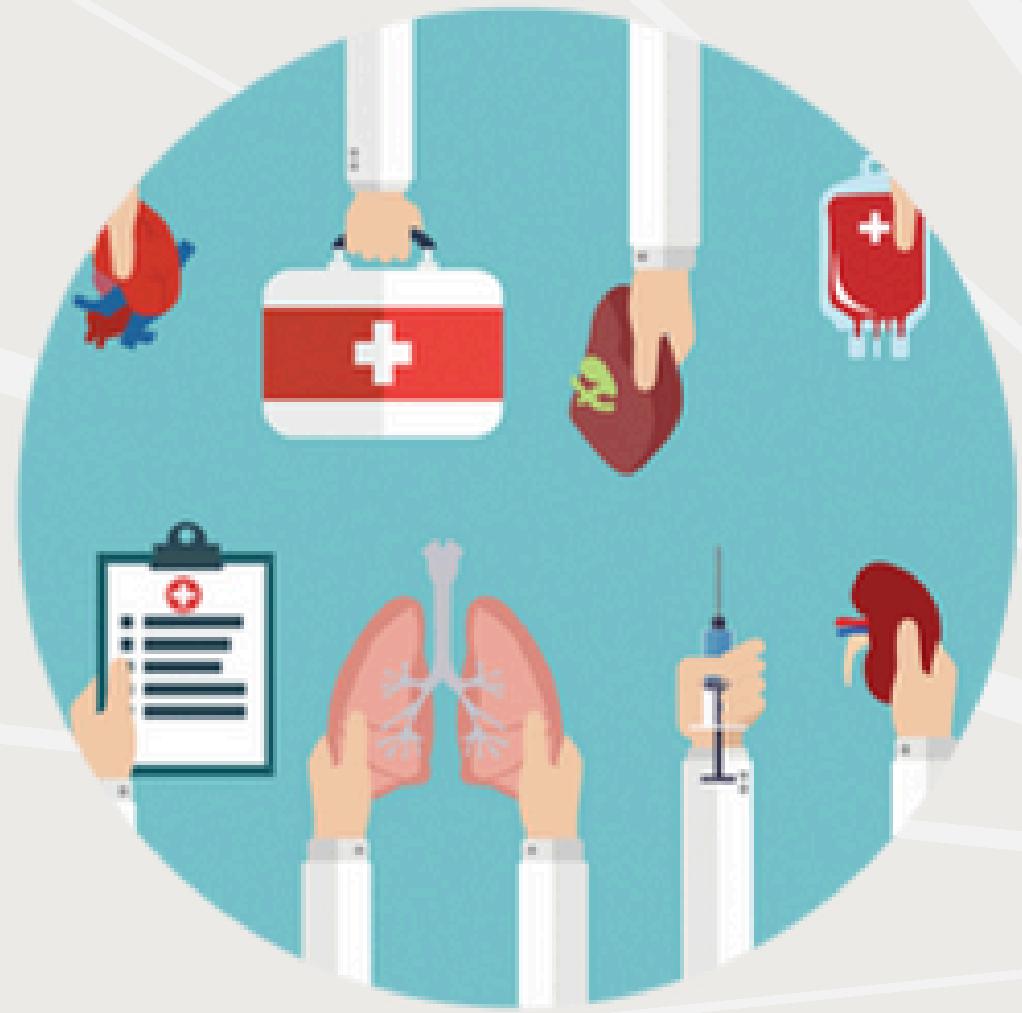
HOW DO THEY WORK?

- Calcineurin inhibitors: function by blocking the production of cytokines. Calcineurin (a protein) is required for T-cell activation.
- Antimetabolites : They interfere with the production of DNA and RNA hence hindering the proliferation of immune cells. Sirolimus inhibits mTOR (protein) which plays a key role in the proliferation and survival of T-cells.
- Corticosteroids: They mimic the actions of natural hormones produced by the adrenal gland.

06 | IMMUNOSUPPRESSANTS

They: -

- Reduce cytokine production.
- Inhibit migration of immune cells.
- Reduce activation of T and B cells.
- They also stabilize cell membranes and this reduces the release of inflammatory mediators from cells.
- Antibodies: Antibodies such as basiliximab and rituximab target specific proteins on the surface of immune cells. Basiliximab targets a protein called IL-2 receptor, which is expressed on activated T cells. Rituximab targets a protein called CD20, which is expressed on B cells. By targeting these proteins, these antibodies can reduce the activation and proliferation of T cells and B cells.



CHALLENGES IN ORGAN TRANSPLANTATION



ORGAN SHORTAGE

the major sources of organs are deceased donors after brain death; however, a substantial number of organs come from live donations, and a significant number can also be obtained from non-heart-beating donors. Donors should be relatively closed that's why organ transplant still suffer .



IMMUNE REJECTION

Rejection is caused by the immune system identifying the transplant as foreign, triggering a response that will ultimately destroy the transplanted organ or tissue . this was very issue how doctors and scientist solve the problem we will see later .

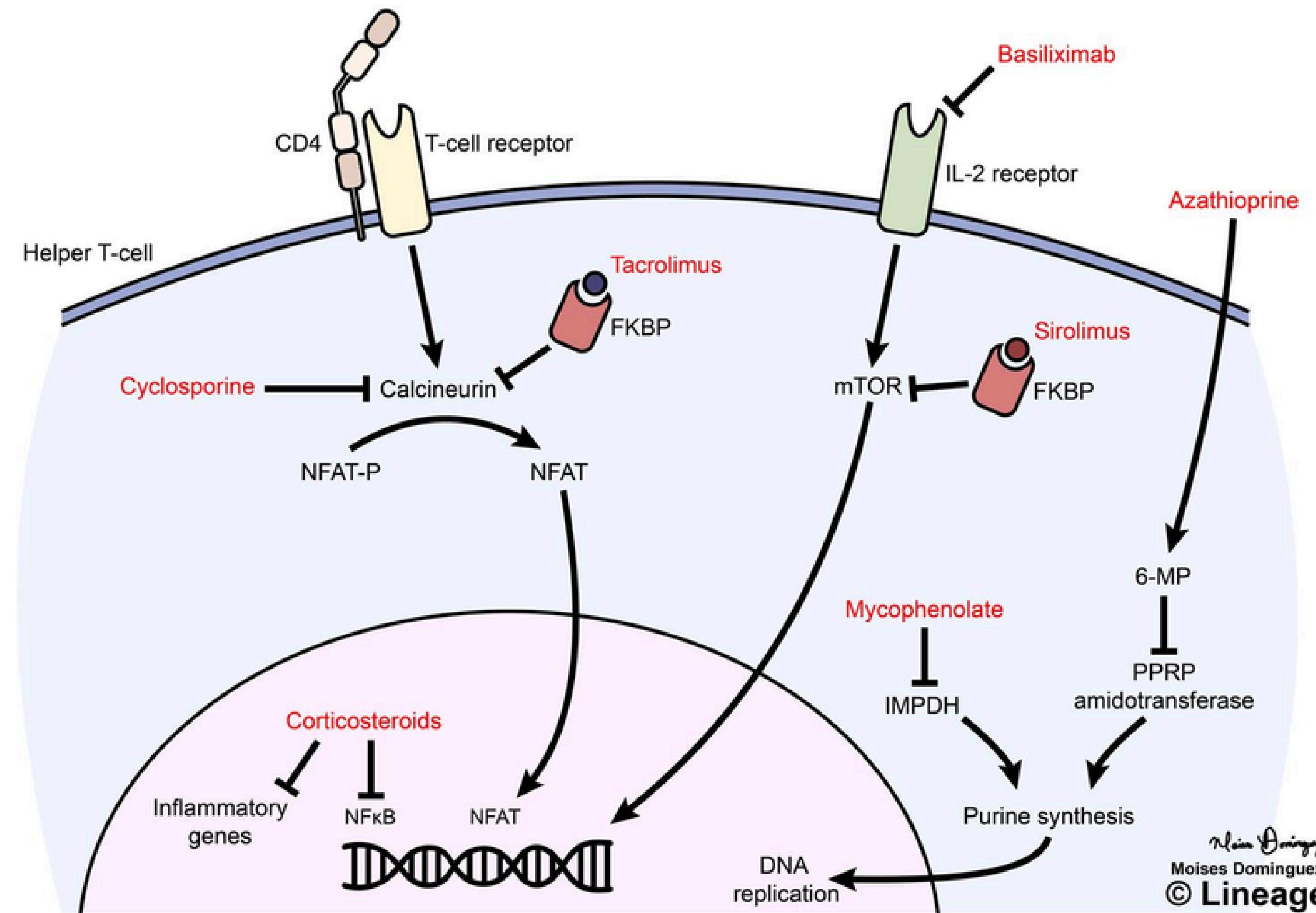


ETHICAL ISSUE

Organ donation by living donors clearly saves lives, improves transplantation outcomes under some circumstances, and reduces recipients' waiting times. It also increases opportunities for patients without living donors to receive organs from deceased donors. However, it raises a series of ethical questions that have not been fully addressed.

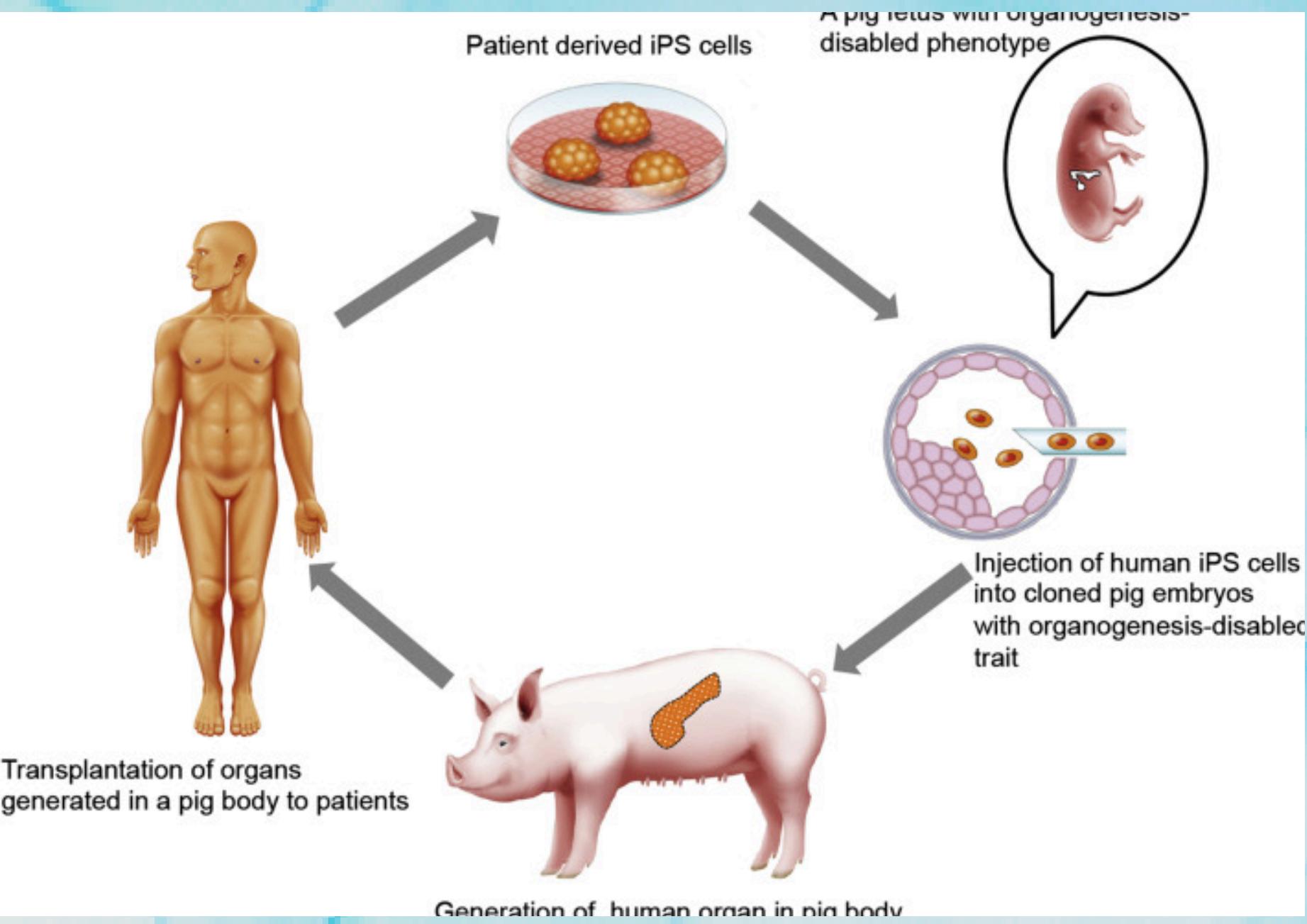


Targets of Select Immunosuppressants



The future of organ transplantation

1. Generation of functional organs from stem cells



- Stem cells are undifferentiated cells found in the body which have the ability to continuously divide, self-renew themselves and differentiate into various kinds of cells. With the capability of self-renewal, pluripotency and differentiation.
- **However, the severe shortage of donor organs has become the main obstacle to expand the organ transplant program. Generation of biological or semi-biological organs could be an alternative approach to solve the problem of the donor organ shortage. Notably, researchers have been hunting for ways to establish a whole organ using stem cells.**

2 .formation of Bioartificial organs

- A device available on demand that can be implanted or integrated into a human body – interfacing with living tissue – offers the possibility to restore defective/failed organs, either temporarily or permanently.
- Recent advances in biomaterials, innovation in processing technologies, highly durable devices, progresses in the decellularization of animal tissue and organs, and cell-based therapies have brought bioartificial organs closer to realization in clinics.
- Physiologically relevant organ substitutes result from the merging of heterogeneous cell types with multifunctional materials to recapitulate native organ geometries, components, and functions.

