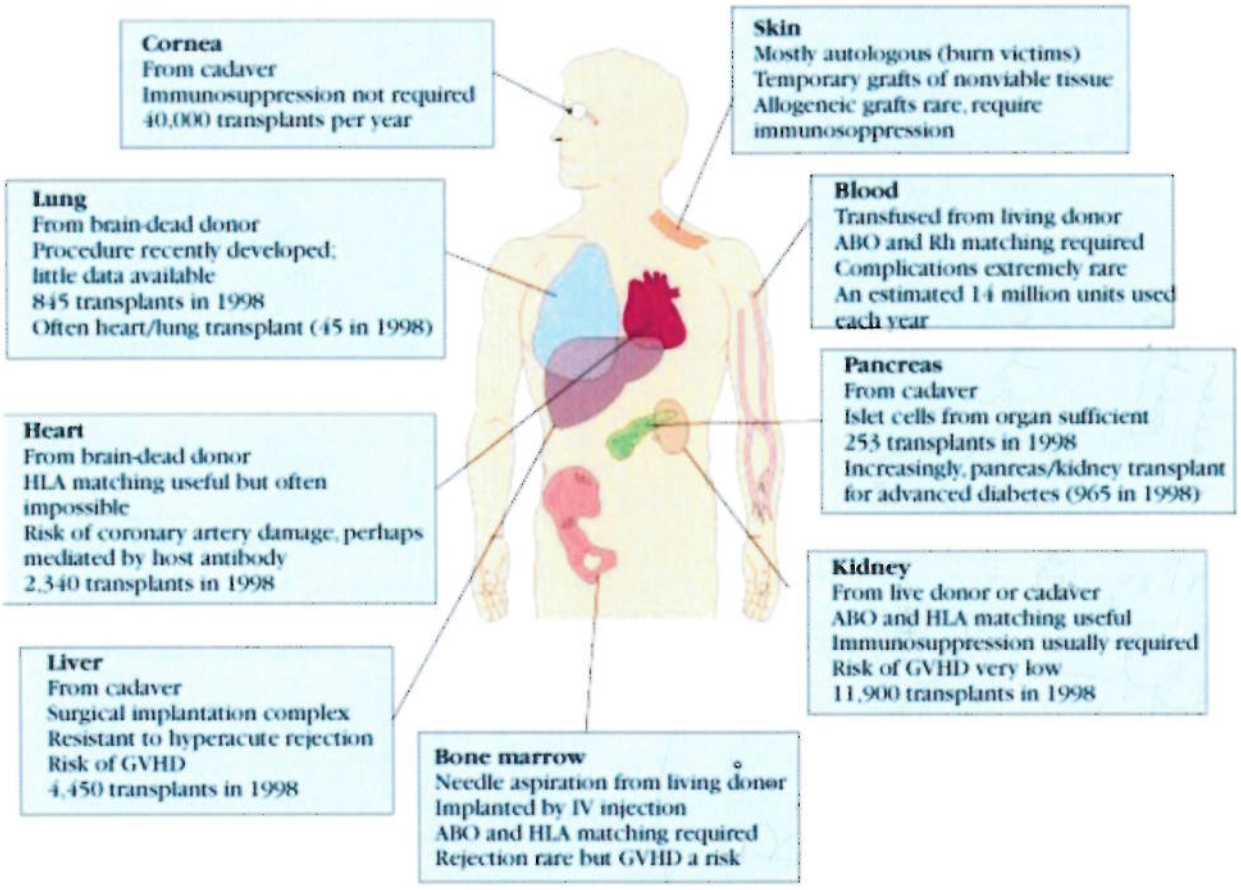
Transplantation Immunology

Key Terms:

- Autograft
- Isograft
- Allograft
- Xenograft
- GVHD
- Hyper-acute rejection
- Primary acute rejection
- Secondary acute rejection
- Chronic rejection
- alloantigen
- Type II hypersensitivity (ABO)
- Type IV hypersensitivity (MHC)

Transplantation is the transfer of cells, tissues or organs (**graft**) from one individual (**donor**) to another (**recipient or host**) to rectify a disease situation.



Types of Grafts / Transplants

Autograft - from one part of the body to another.

Isograft - between two genetically identical individuals.

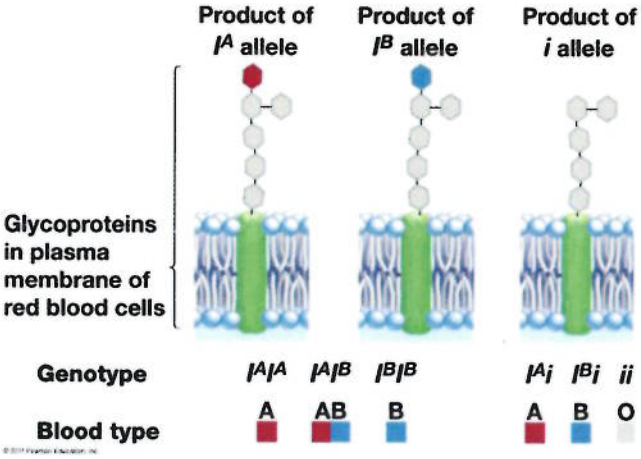
Allograft - between two genetically dissimilar individuals of the same species. ← most common

Xenograft - between two species. PIG (heart valves)

Autografts and isografts are accepted due to genetic identity between donor and recipient. Allograft is genetically dissimilar from the recipient and therefore is recognized as foreign by the immune system and rejected. Xenografts involve the maximum genetic dissimilarity and therefore a vigorous immune response is mounted against the graft.

Blood transfusion

i) Major blood group antigens: A, B, O
ii) Cell surface polysaccharides on RBC and vessel endothelium
iii) O – shortest polysaccharide
A & B differ in terminal sugar residue.
iv) Genetics:
I^A – sugar A is attached
I^B- sugar B is attached
i – no sugar is attached.
v) Individual doesn't produce Ab against own blood group.
vi) Cross-reacting pre-existing antibodies cause **hyper-acute** rejection.

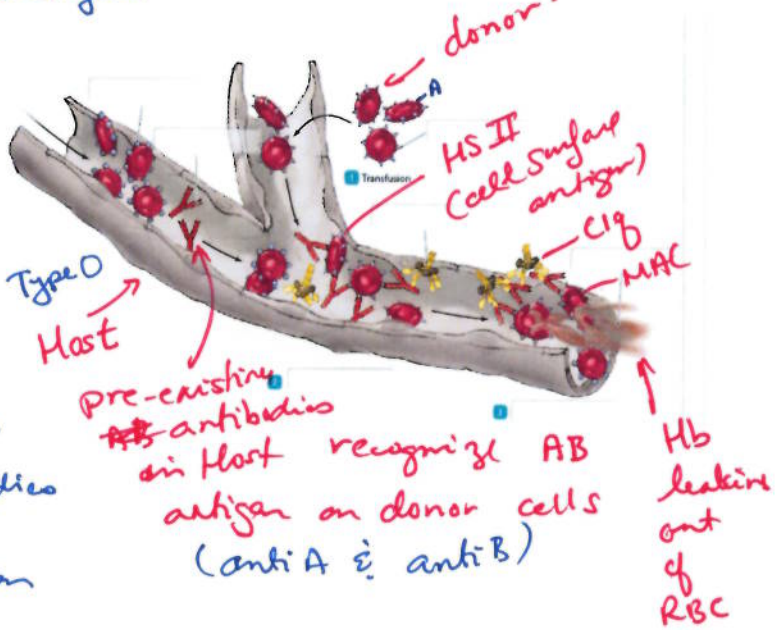


Where did the antiA/B antibodies come from?

– raised against common pathogens, cross-react with blood group antigens.

vii) RBC introduced by transfusion are agglutinated by pre-existing antibodies.
vii) RBC destroyed by complement activation, NK cell activity

Genotype	Phenotype	Ab present
ii	O	Anti A / Anti B
I^Ai or I^AI^A	A	Anti B
I^Bi or I^BI^B	B	Anti A
I^AI^B	AB	no ~~Ab~~ antibodies



Universal Recipient: AB – no antibodies

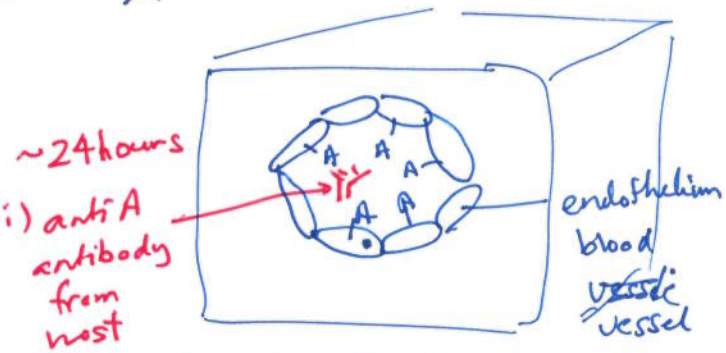
Universal donor: O – no antigens on the RBC

Solid Tissue Rejection

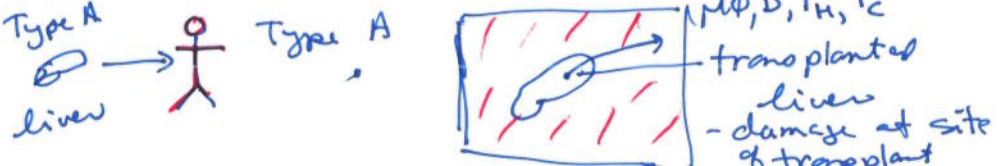
A. Hyperacute rejection
(Type II hyper-sensitivity)

Type A Liver → Type O (anti A / anti B)

- Uncommon, blood types are usually correctly matched.
- Occurs within 24 hours of transplantation.
- Blood group markers are found on the surface of blood vessels.
- Pre-existing antibodies, specific for graft antigens, bind to endothelia wall. Complement activation followed by massive recruitment of neutrophils occurs followed by rapid inflammation of the transplanted tissue.
- Without blood source, tissue dies.

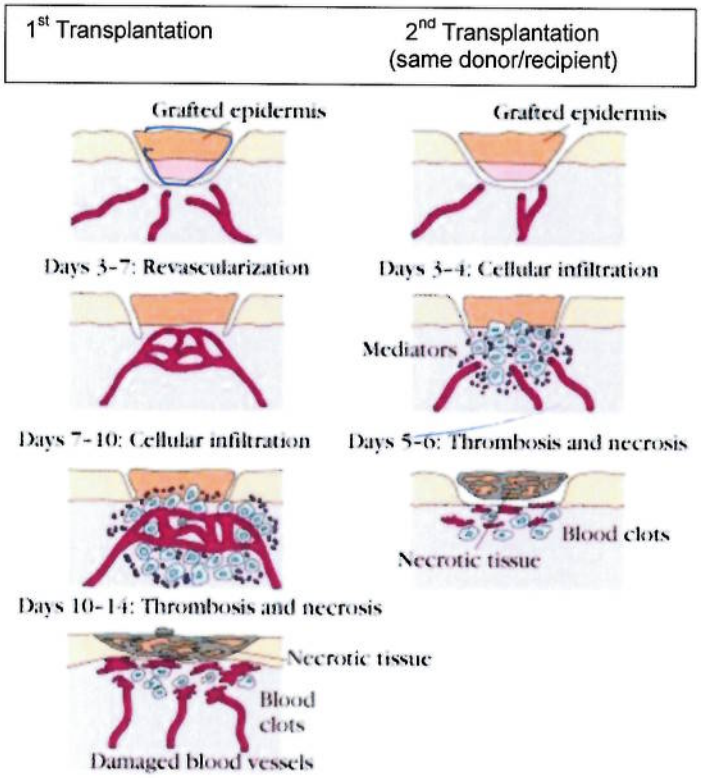


B. GVHD: Graft versus host disease. Graft recognizes host as foreign due to the immune cells that came along with the transplanted tissue.



C. Acute rejection:

- Most common (blood types are usually correctly matched).
- Speed/extent of rejection depends on MHC mismatch
- Can be suppressed by immunotherapies.



• memory cells
B, T_H, T_C

• what is the antigen?
MHC (HLA)

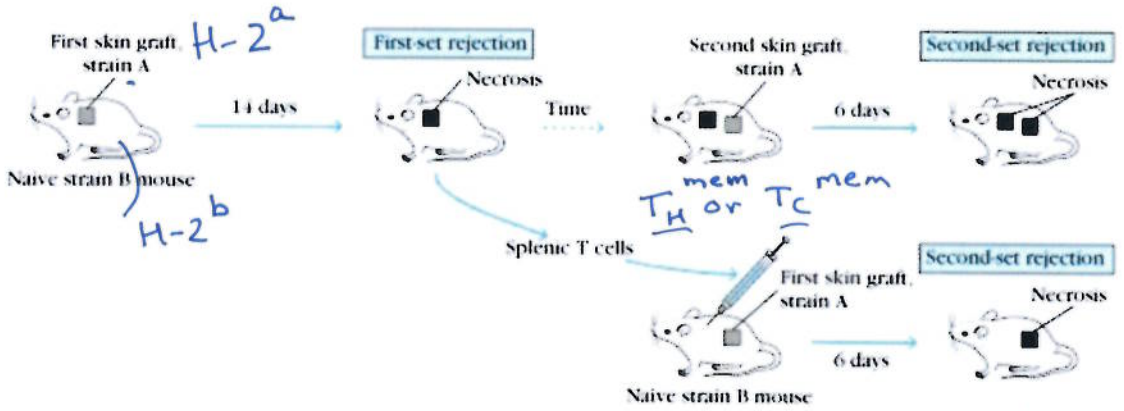
Evidence that MHC (HLA) and T cells are involved in Acute Rejection.

i) Skin grafts:

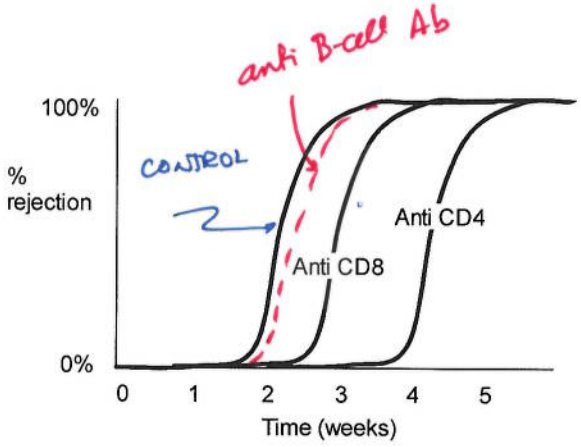
Donor	Recipient	Outcome
H-2^b	H-2^b	Accepted
H-2^k	H-2^k	Accepted
H-2^b	H-2^k	Rejection

ii) Immunological Memory via T-cells: Transferred T^{MEM}-cells generate 2^{ndy} response in naïve transplants.

iii) Which T-cells are more important, T_H or T_C?



The time to rejection for mouse skin transplants are shown on the right. The mice were injected with no antibodies, or anti-CD8 antibodies or anti-CD4 antibodies



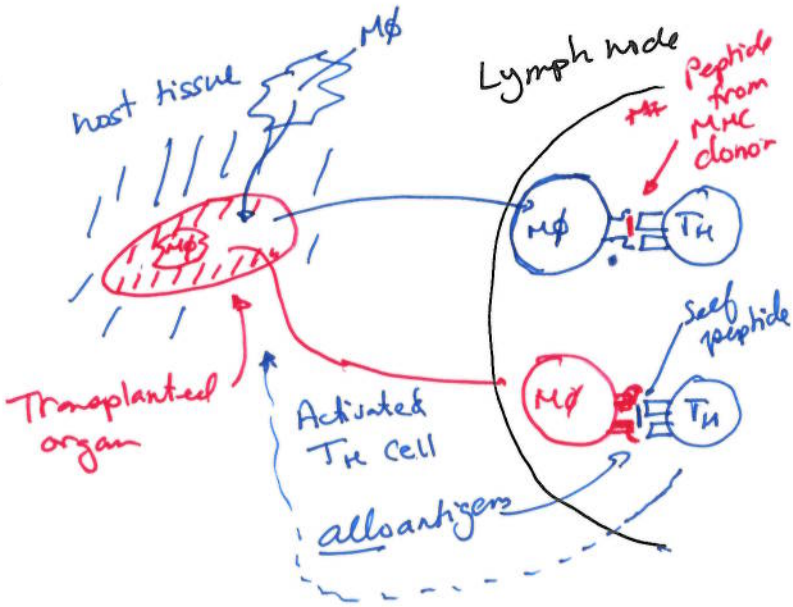
- Anti CD4 Ab will interfere with T_H function.
→ ⇧ largest delay in rejection

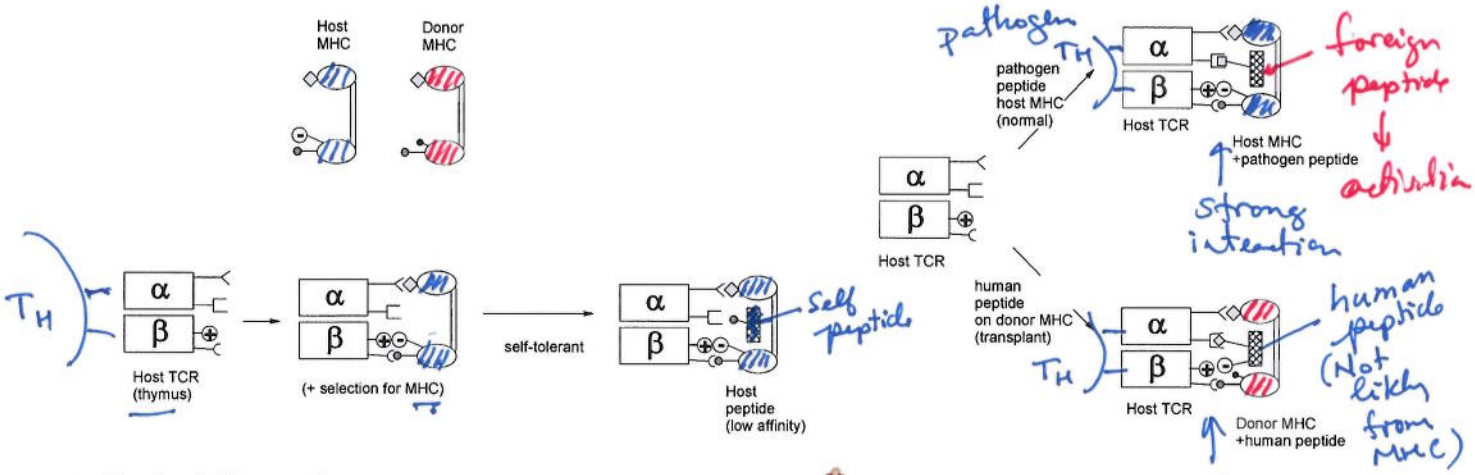
T_C are also involved, but to lesser extent.

T-cells Sensitization:

1. Revascularization of graft occurs (3-7 days). This allows host cells to enter graft and donor cells to leave the graft.

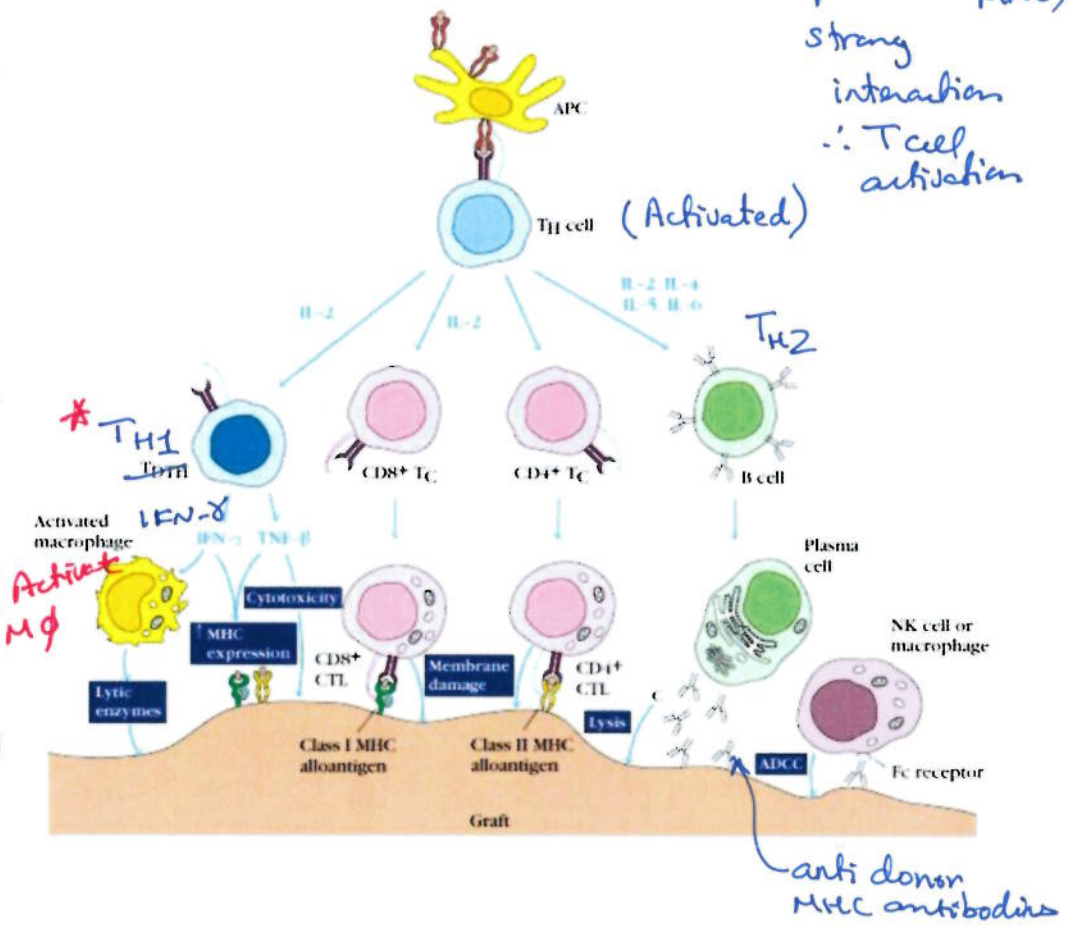
- Host APC cells ingest donor tissue and present foreign peptides, such as MHC I and II. Activate host T_H – cells, via the "normal" T-cell response, in this case the foreign peptide is simply a different allele from the host MHC proteins, *a foreign peptide.*
- High concentration of surface MHC on the donor APCs causes a small number of T_H (MHC II) and T_C cells (MHC I) to bind to the *foreign(donor)* MHC/peptide complex (***alloantigen***) , thinking that they are actually interacting with self (host)-MHC + foreign peptide, when they are interacting with a foreign MHC + self-peptide.





Activation/Effector phase:

1. The MHC/peptide T-cell interaction leads to clonal expansion of a sub-population of T cells into active T_H1, T_H2, and T_{CTL}.
2. The **T_H1 response** is by far the **most important**. T_H1 cells secrete **IFN-γ, activating macrophages.**
3. T_{CTL}cells, recognizing MHC I alloantigens, lead to membrane damage.
4. Antibodies, produced from a T_H2 response, can cause tissue damage due to complement lysis. Antibodies can also lead to ADCC (antibody dependent cell-mediated cytotoxicity) via NK cells.



D. Chronic rejection

Occurs months or years after transplantation

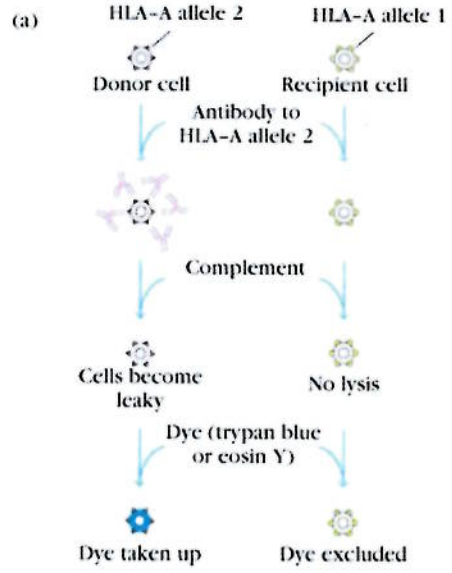
- Includes both humoral and cell mediated responses.
- Difficult to suppress.

Tissue Typing for Transplantation:

Blood Group Antigens – These should be tested first, to prevent hyperacute rejection.

HLA (MHC) typing: To test compatibility between donor and recipient. **a) Serologic Typing**

- HLA molecules on donor and recipient lymphocytes are identified using specific monoclonal antibodies and complement.
- Lysis by complement indicates presence of HLA molecule on the lymphocyte
- HLA markers of donor and recipient are compared.
- Quick and fairly reliable test (i.e. can be used for heart transplants)
- Limited by availability of a range of monoclonal antibodies against assorted HLA molecules



Antibody to different HLA-A antigens

	1	2	3	4	5	6
Recipient	●	○	○	○	●	○
Donor 1	○	●	○	○	●	○
Donor 2	●	○	○	○	●	○
Donor 3	○	○	●	○	○	○

⊕ fast
⊖ can't test all alleles. (large # of them)

b) Mixed Lymphocyte Reaction (MLR)

i) Donor and recipient lymphocytes plus ^{3}H thymidine; donor lymphocytes are irradiated to prevent the reaction of the donor cells by the recipient

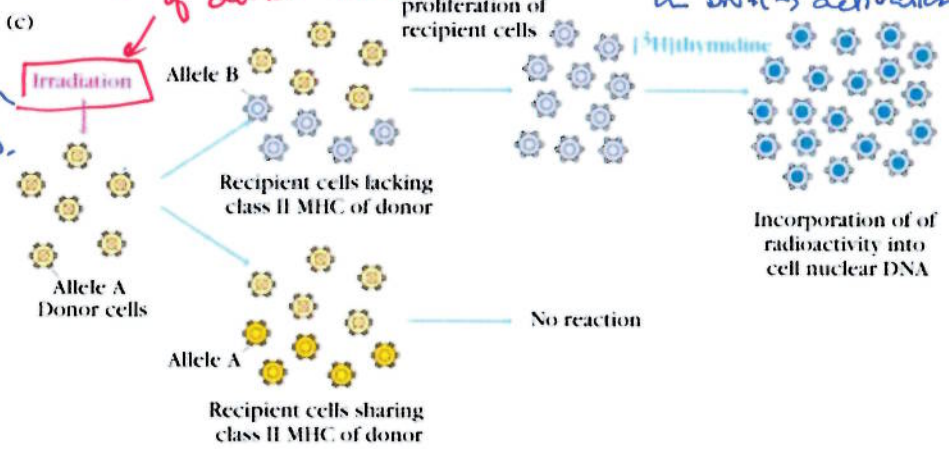
ii) If recipient lymphocytes recognize donor lymphocyte HLA molecules as foreign, they are activated and begin to proliferate

iii) Proliferation detected by uptake of ^{3}H thymidine

iv) Slow but comprehensive test. Quantitative assay - extent of proliferation indicates how antigenically dissimilar or histoincompatible the donor and recipient are. *This is one of the best predictors of whether the graft will be accepted.*

prevents activation of donor cells

high radioactivity in DNA → activation.

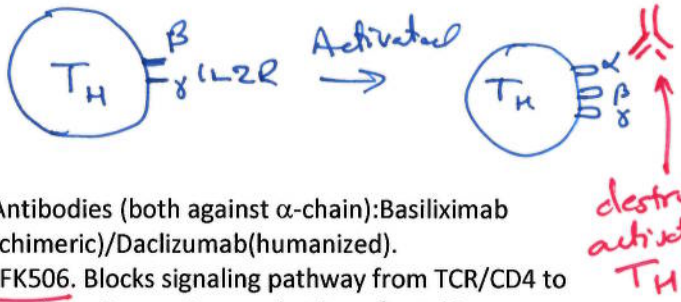


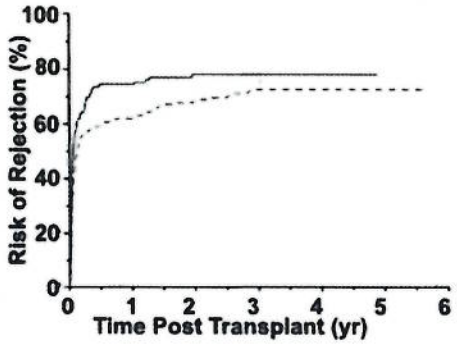
⊕ detects activation of host T cells.

⊖ Slow, 2-5 days

Immunosuppressant Therapy - Pittsburgh Protocol:

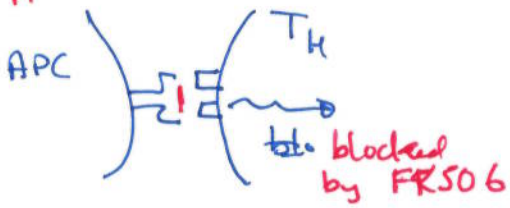
1. Treatment of anti-IL2 receptor antibodies immediately after transplant (antibody induction therapy)
   IL2 receptor:
   βγ – low affinity, constitutive receptor
   αβγ – high affinity, α chain produced by activated T-cells.



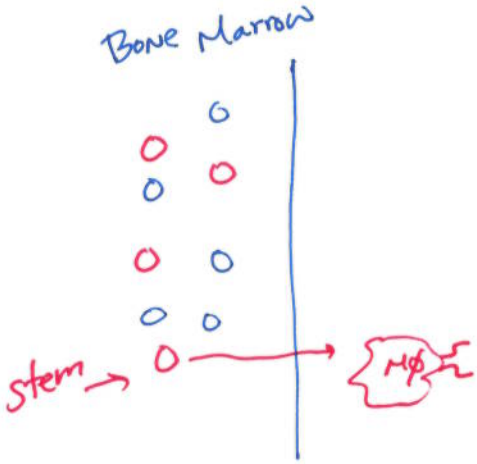


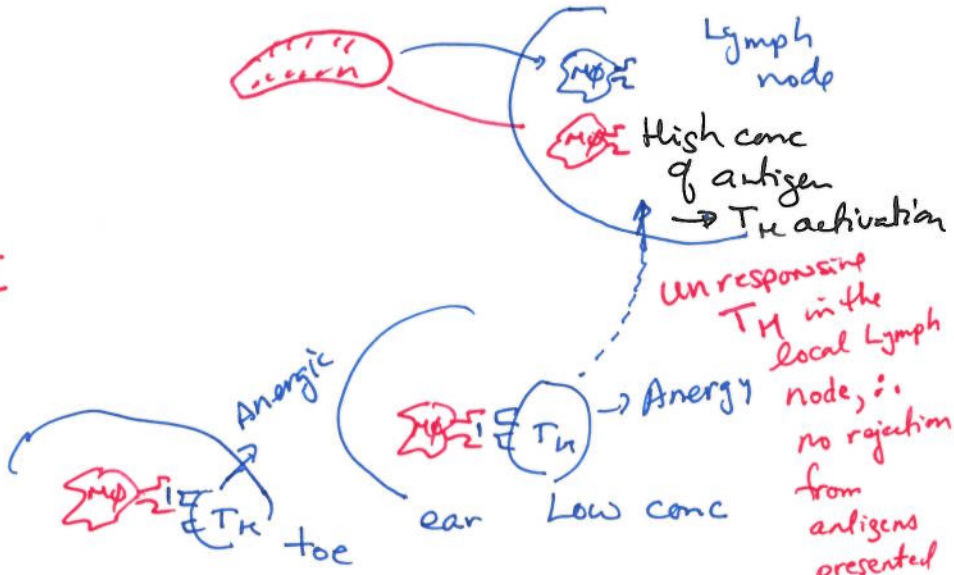
Infusion of donor leukocytes to induce tolerance in organ allograft recipients (1999) Salgar et al, *Journal of Leukocyte biology*, 66, 310-314.

   Antibodies (both against α-chain):Basiliximab (chimeric)/Daclizumab(humanized).
2. FK506. Blocks signaling pathway from TCR/CD4 to nucleus. Preventing production of cytokines.



3. Injection of *donor* bone marrow during, and depending on the organ type, a few days after transplant.



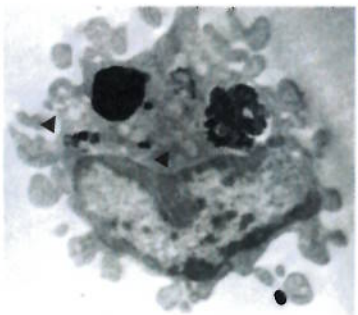


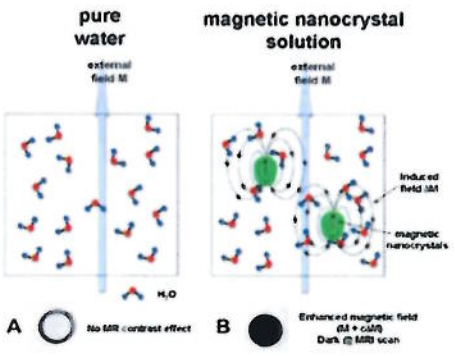
Detection of Rejection:

A. Old/Present– Biopsy

See Next lecture packet

B. Future– Cell tracking and functional Imaging by MRI (Magnetic Resonance Imaging)





(http://bme240.eng.uci.edu/students/08s/ykim30/03.htm)