Immunology of Renal Transplantation

Dr.Hend's NOTES

Dr.Adel's NOTES

Extra Explanation

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 mana

Major Histocompatibility Complex and Transplantation

- 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

Transplantation can be cells or tissue or organs

HLA the other name of MHC, (HLA=MHC)

we call it Alloantigen because it's related to allograft

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

مالها أي علاقه ب transplantation ماعلينا منها

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**				

NO need to memorize numbers

Let's summarize what has written in previous slides

Play important Role IN Rejection

	MHC Class 1	MHC Class II
Gen Products	HLA-A,-B,&-C	HLA-DP,DQ
Cells Distribution	all nucleated cells	antigen presenting cells (macrophages, B cells, dendritic cells and Langerhans cells)
Recognized By	Cytotoxic T cell (CD8+)	Helper T cell (CD4+)

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

We are NOT sure about their ROLE but may

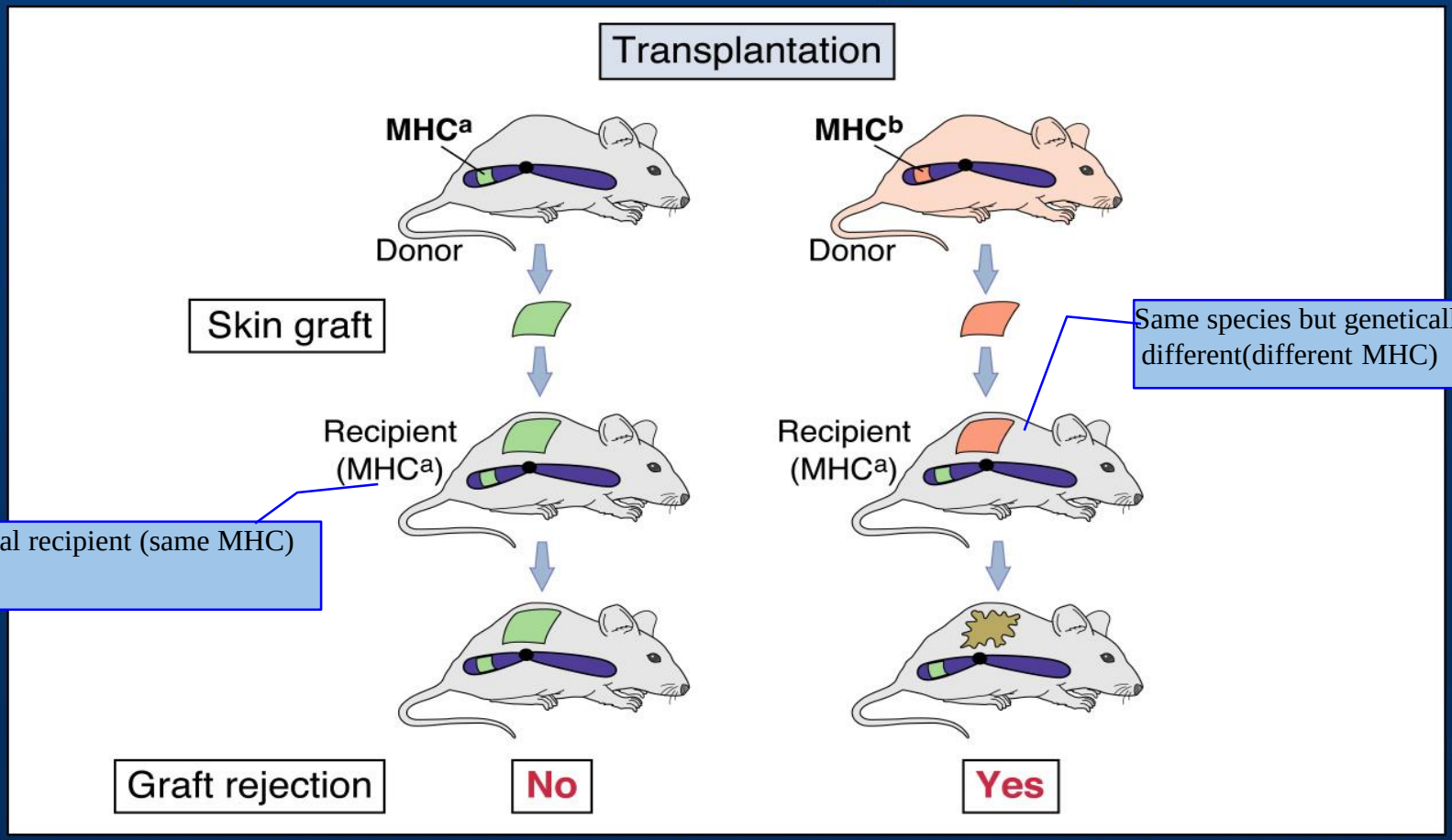
ليس لها دور بحالات الرفض المباشر

مشكلتها اني ماقدر اكتشفها بالمعمل ولا اسويلها اختبار توافق، ويعتقد انها الي دايم يصير الرفض بسببها

Transplantation antigens

Slide 4-2

MHC alleles control allograft rejection



identical recipient (same MHC)

Same species but genetically different(different MHC)

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
    - Tissue returning to same individual after a period outside the body – usually in a frozen state.
    - Common in skin grafting; bone marrow.

نحتد اليه في حالات الحروق

مثال:عند المرضى الي عندهم بوادر إصابة بلوكيميا قبل بدا العلاج الاشعاعي يطلعون البون مارو من الجسم يحفظونه بعد التعرض للعلاج الاشعاعي يرجعونه للجسم

  - Syngeneic grafts or (isograft)
    - Donor and recipient are genetically identical
    - identical twins ,Animal models.

أفضل مثال

by inbreeding animals
تزويج الاقارب من الحيوانات: to increase the probability that the two copies of any given gene will be identical

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

ألأكثر شيوعا

ما زال عليها دراسات

من اسد الى انسان:مثال

Synthetic

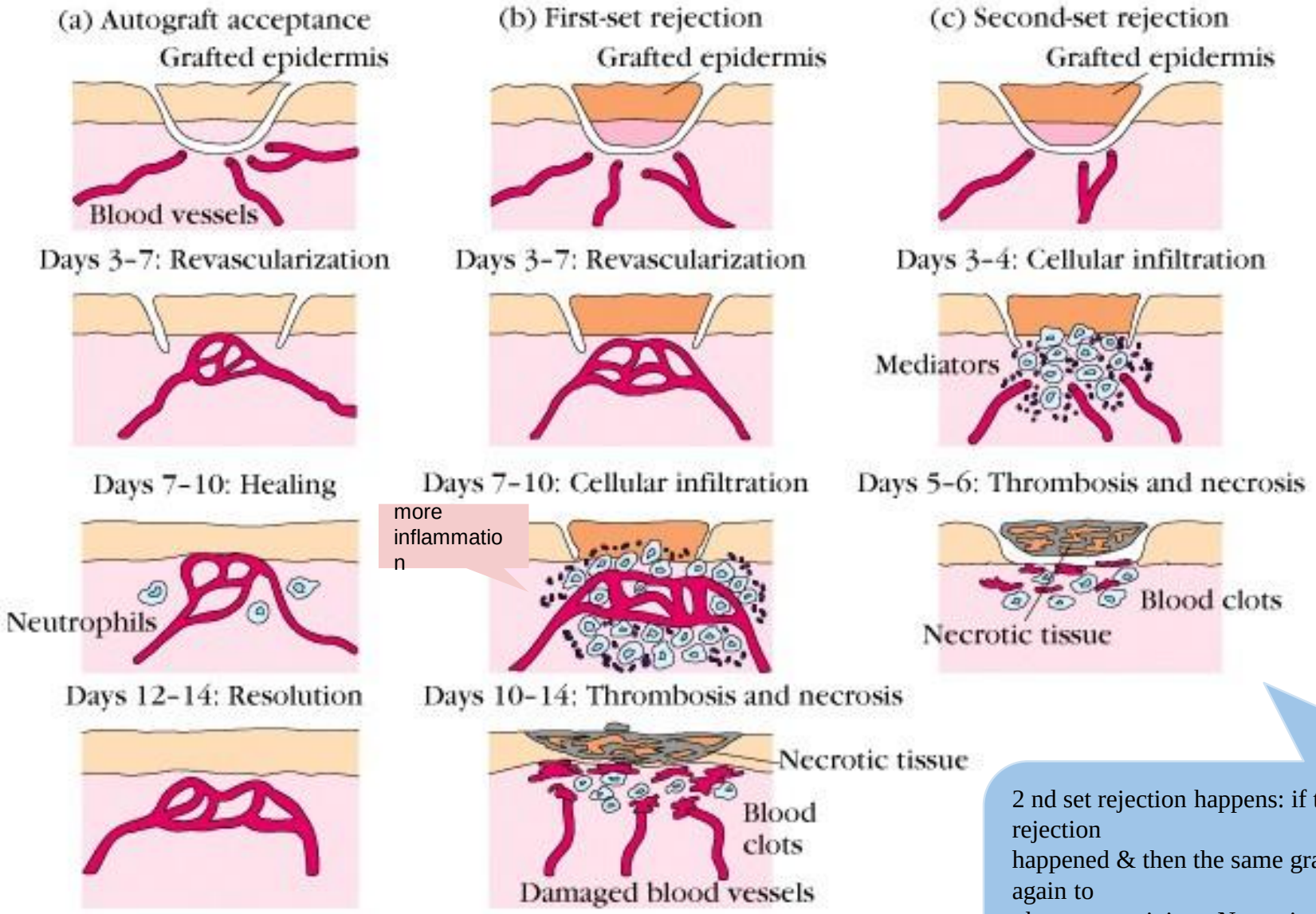
Transplantation (Rejection)

- Rejection: damage done by the immune system to a transplanted organ

- 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

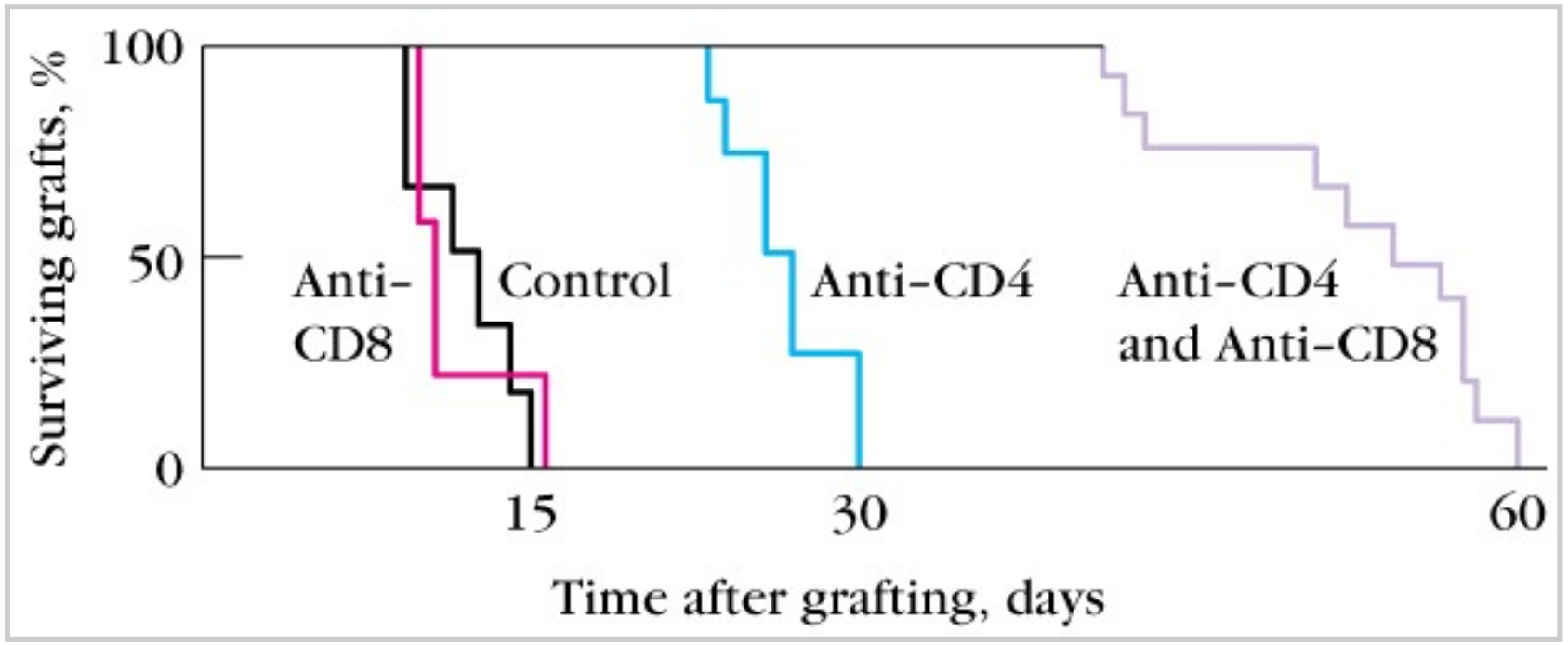
مالها دور كبير

1st set versus 2nd set reactions



2 nd set rejection happens: if the1st set rejection happened & then the same graft is introduced again to the same recipient. Necrosis will happen even faster than the first time. It's known as developing immunity against the graft due to presence of memory cells

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



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

from this experiment we conclude :
If we inhibit the CD4 the tissue will survive longer than inhibiting of CD8 , but if we inhibit
both of them the tissue will survive much longer**(synergic effect)** .
so, **CD4 is more important then CD8**

this experiment indicate to the importance of T cells especially CD4 in Rejection

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

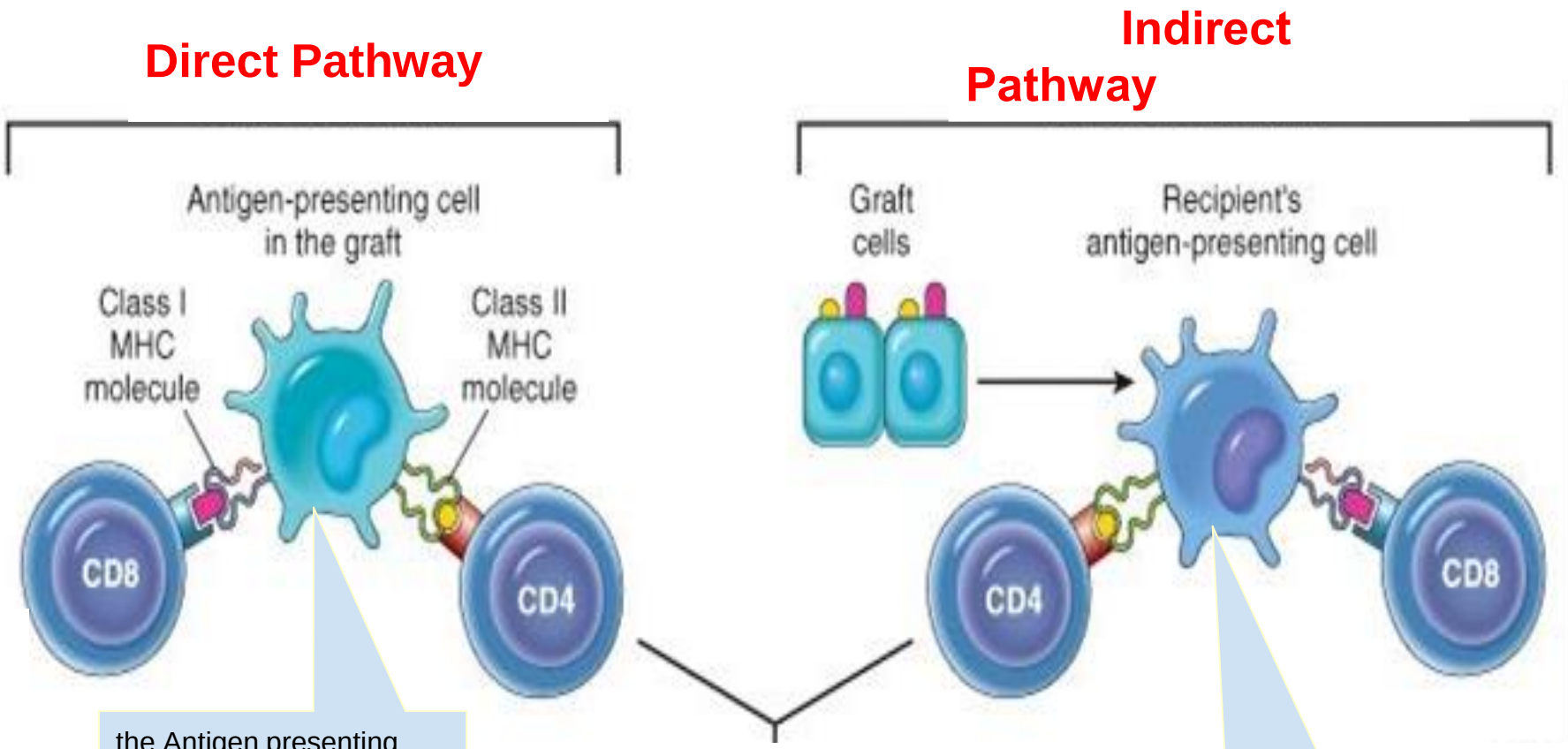
هذه التجربة تعزز دور t cells بالرفض

هذه التجربة تثبت ان Antibodies لا تلعب دور مهم بالرفض

فإران طبيعتها ماعندها thymus>no maturation of T cells

Nude mouse has a transplant of rabbit skin

Mechanisms involved in Graft Rejection



Rejection Response

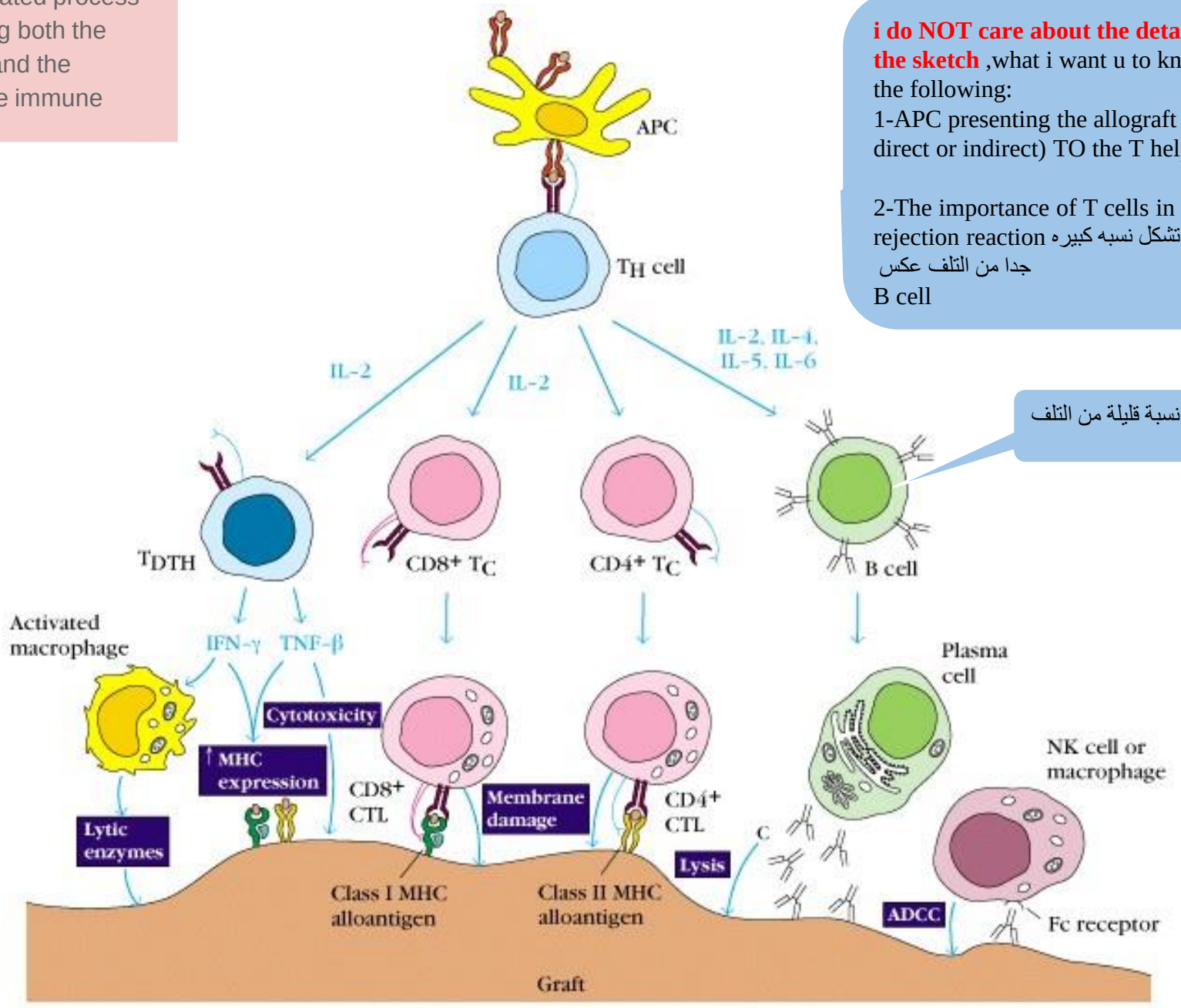
Rejection is a complicated process involving both the innate and the adaptive immune system

i do NOT care about the details in the sketch ,what i want u to know is the following:

1-APC presenting the allograft (either direct or indirect) TO the T helper cell

2-The importance of T cells in the rejection reaction كيف انها تشكل نسبه كبيره جدا من التلف عكس B cell

لا تشكل الا نسبة قليلة من التلف



Clinical manifestations of graft rejection

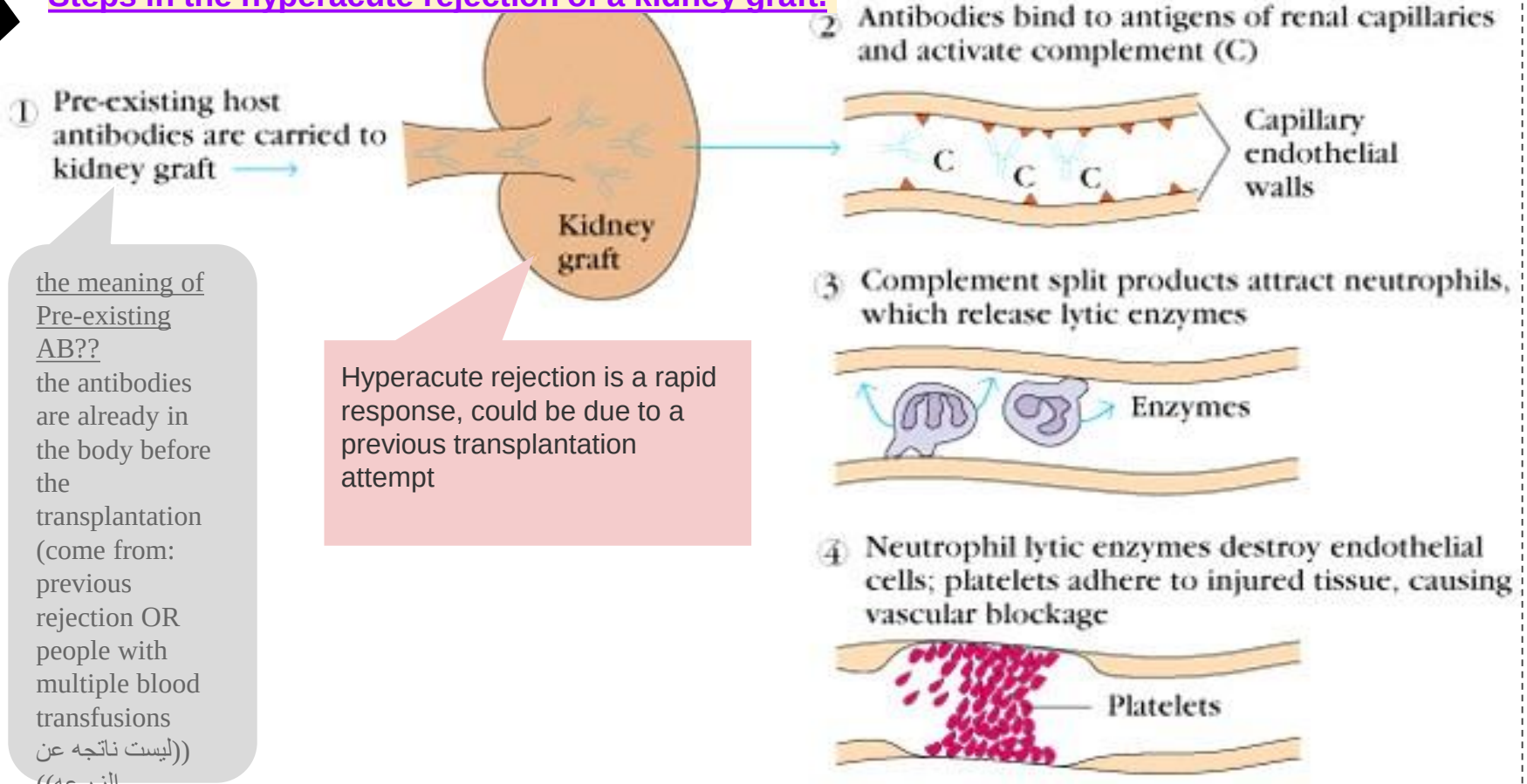
I. Hyperacute rejection: very quick

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

III. Chronic rejection: months-years (both) (cell & Ab mediated)

caused by : preexisting host serum antibodies specific for antigens of the graft. Occur ONLY if the preexisting antibodies have the ability to cross react with the graft

Steps in the hyperacute rejection of a kidney graft.



Hyperacute rejection is a rapid response, could be due to a previous transplantation attempt

the meaning of Pre-existing AB??
the antibodies are already in the body before the transplantation (come from: previous rejection OR people with multiple blood transfusions
(ليست ناتجه عن

Chronic Rejection

- This occurs months to years after engraftment
- Main pathologic finding in chronic rejection is atherosclerosis of the vascular endothelium

why there is atherosclerosis?
recipient T cells react and secrete cytokines Lead to proliferation of vascular smooth muscle >atherosclerosis

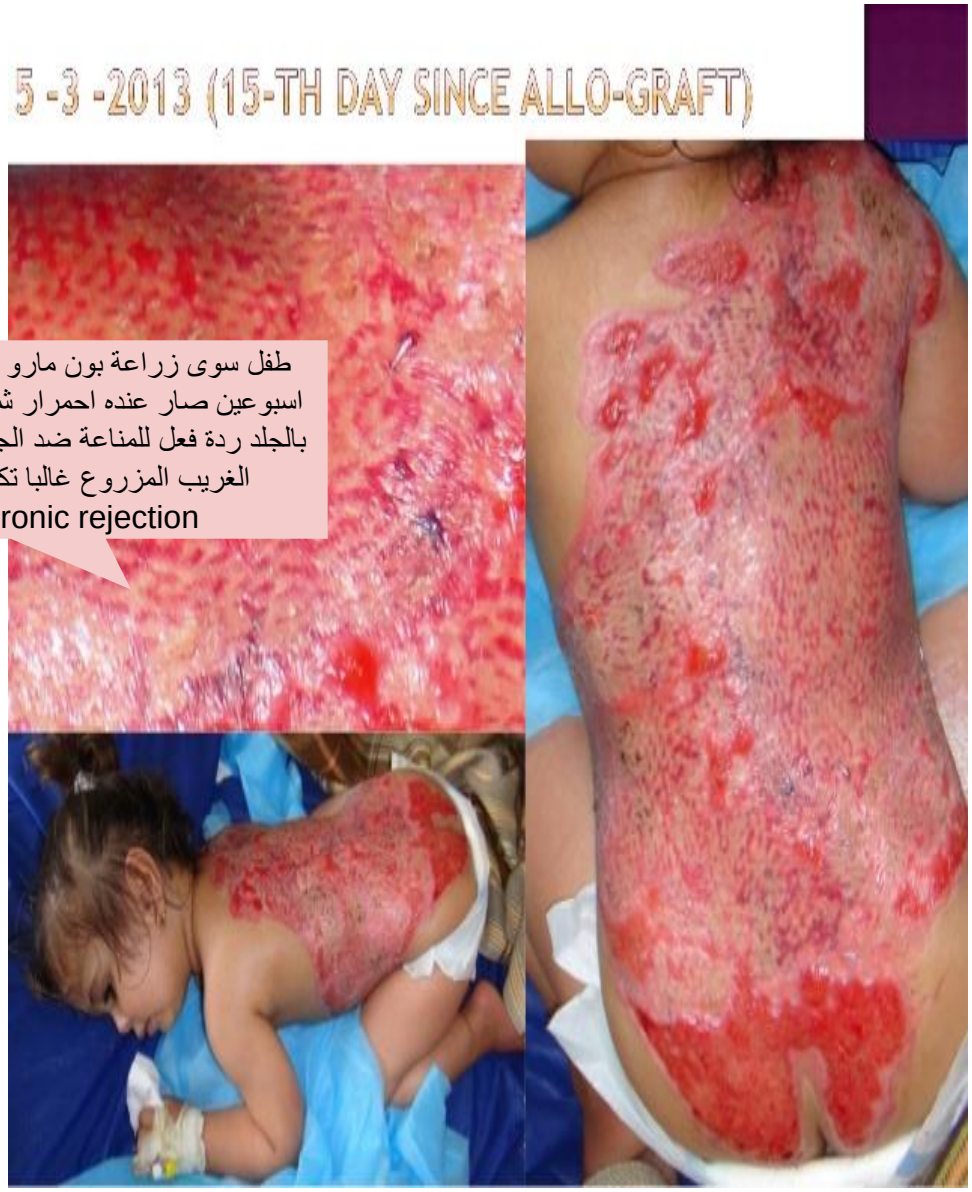
- Main cause of chronic rejection is not known.
- Minor histo-compatibility antigen miss match

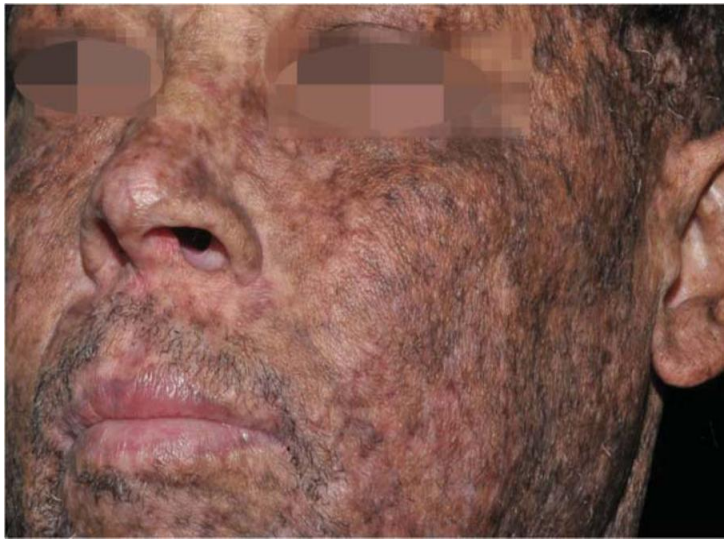
not sure but
Can be due to:

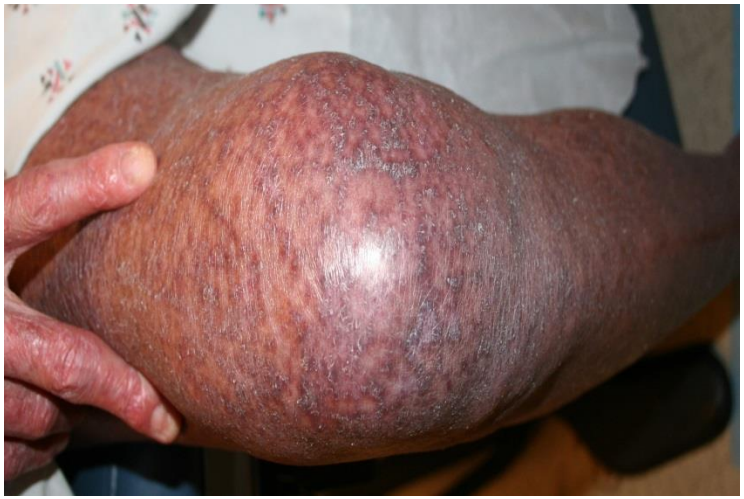
graft attacking the recipient

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


5 -3 -2013 (15-TH DAY SINCE ALLO-GRAFT)
طفل سوى زراعة بون مارو بعد اسبوعين صار عنده احمرار شديد بالجلد ردة فعل للمناعة ضد الجسم الغريب المزروع غالبا تكون
chronic rejection





طرق فحص التوافق النسيجي بالمعمل

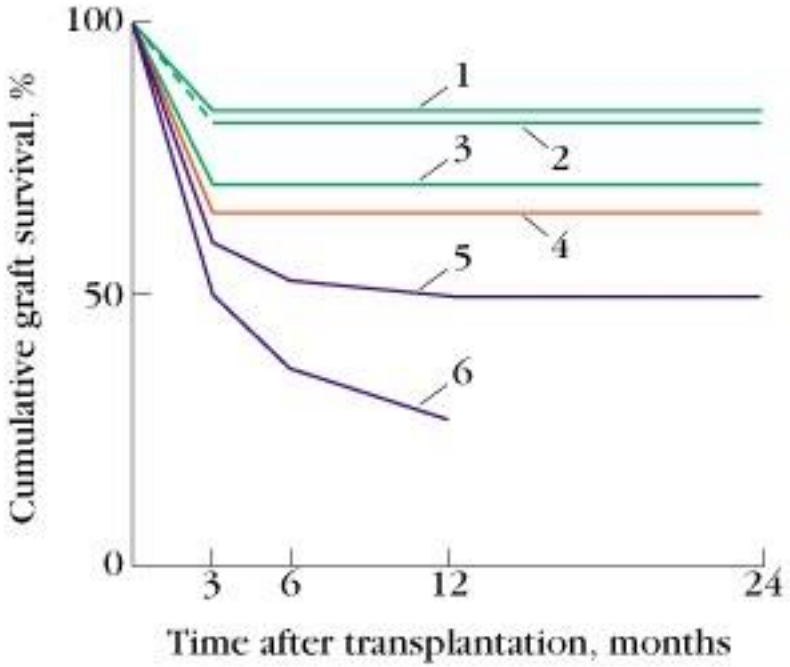
HLA Typing in the Laboratory

- 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
- <u>Methods</u>
  - DNA sequencing by Polymerase Chain Reaction (PCR)
  - Serologic Assays
  - Crossmatching – (Donor) lymphocytes +(Recipient) serum + complement.
  - Mixed Lymphocyte Reaction (MLR)

mixing the lymphocytes of both donor and recipient → 3-4 days → if there is multiplication of cells →no transplantation

Tissue Matching

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



from this experiment :
If there is mismatching in :
*Class I & II >the survival will be very low .
*Class I only >the survival not affected very much.
*Class II only > the survival will be low about 50%.

تدل على أهمية
Class II IN THE REJECTION

عدد عدم التوافق

Curve no.	HLA mismatches (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

Cornea : we don't give immunosuppressant because it's avascular >no rejection will occur.

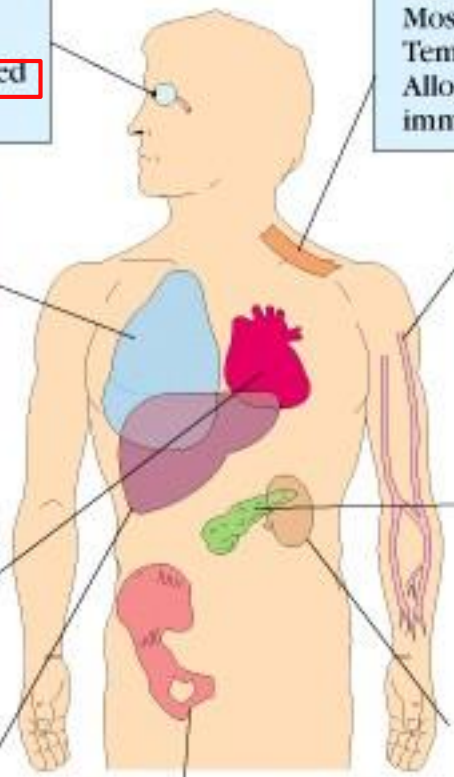
cornea non nucleated there is NO MHC

Cornea
From cadaver
Immunosuppression not required
40,000 transplants per year

Skin
Mostly autologous (burn victims)
Temporary grafts of nonviable tissue
Allogeneic grafts rare, require immunosoppression

Lung
From brain-dead donor
Procedure recently developed; little data available
845 transplants in 1998
Often heart/lung transplant (45 in 1998)

Blood
Transfused from living donor
ABO and Rh matching required
Complications extremely rare
An estimated 14 million units used each year



Pancreas
From cadaver
Islet cells from organ sufficient
253 transplants in 1998
Increasingly, panreas/kidney transplant for advanced diabetes (965 in 1998)

Heart
From brain-dead donor
HLA matching useful but often impossible
Risk of coronary artery damage, perhaps mediated by host antibody
2,340 transplants in 1998

Kidney
From live donor or cadaver
ABO and HLA matching useful
Immunosuppression usually required
Risk of GVHD very low
11,900 transplants in 1998

Liver
From cadaver
Surgical implantation complex
Resistant to hyperacute rejection
Risk of GVHD
4,450 transplants in 1998

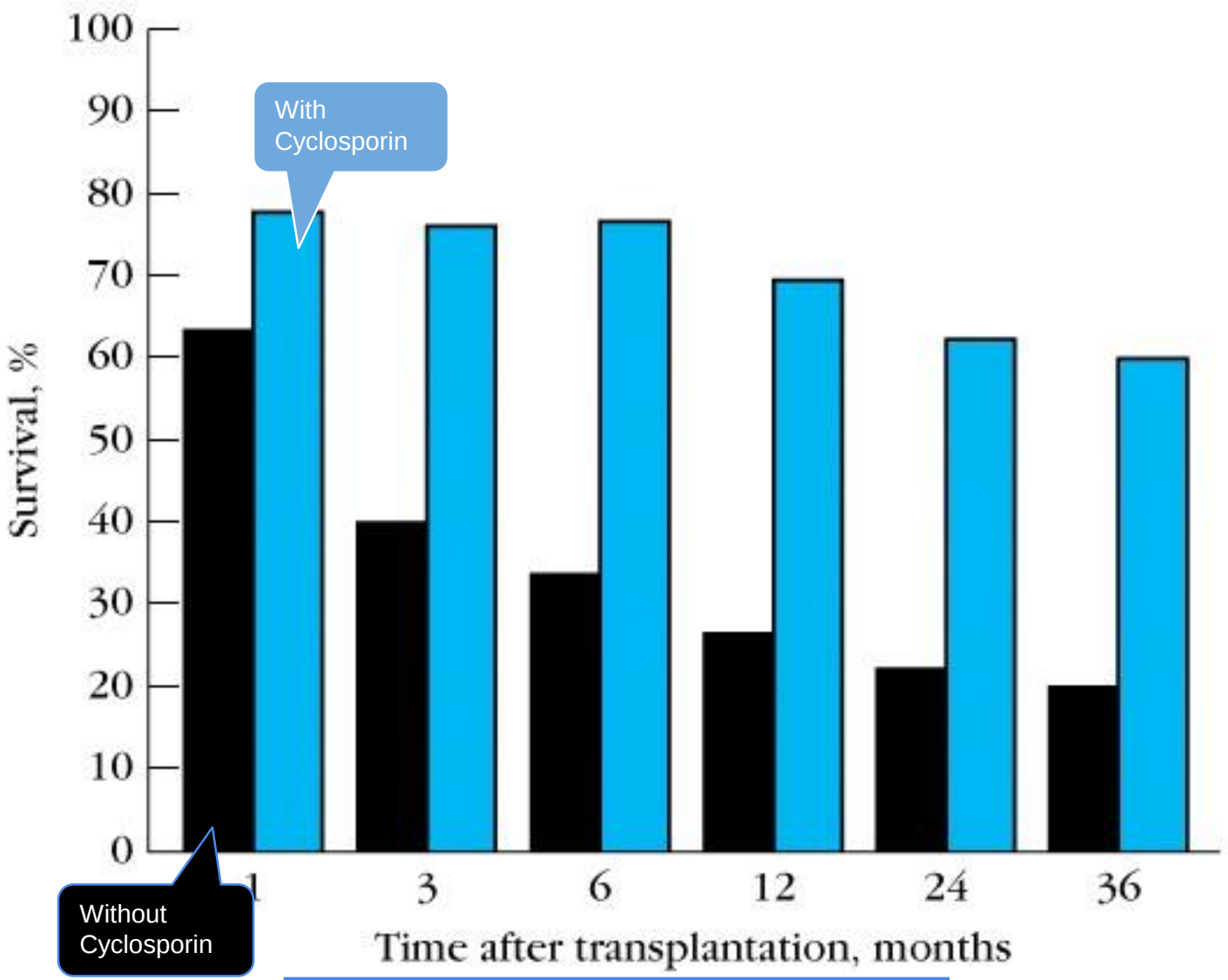
Bone marrow
Needle aspiration from living donor
Implanted by IV injection
ABO and HLA matching required
Rejection rare but GVHD a risk

What I want u to know is the following :
-**bone marrow =** tissue matching is require
-**Kidney=** tissue matching is NOT require BUT useful
-**cornea=**tissue matching NOT require because it's NOT vascularized ,Risk of rejection is ABSENTE

General Immunosuppression Therapy

1) Mitotic inhibitor: azathioprine (pre & post)
2) Corticosteroids — Not specified inhibit the whole immunity
3) Cyclosporin — It is Fungal metabolite that inhibit Tcells Growth factor(IL-2)
4) Total lymphoid irradiation

Immunosuppresive Therapy

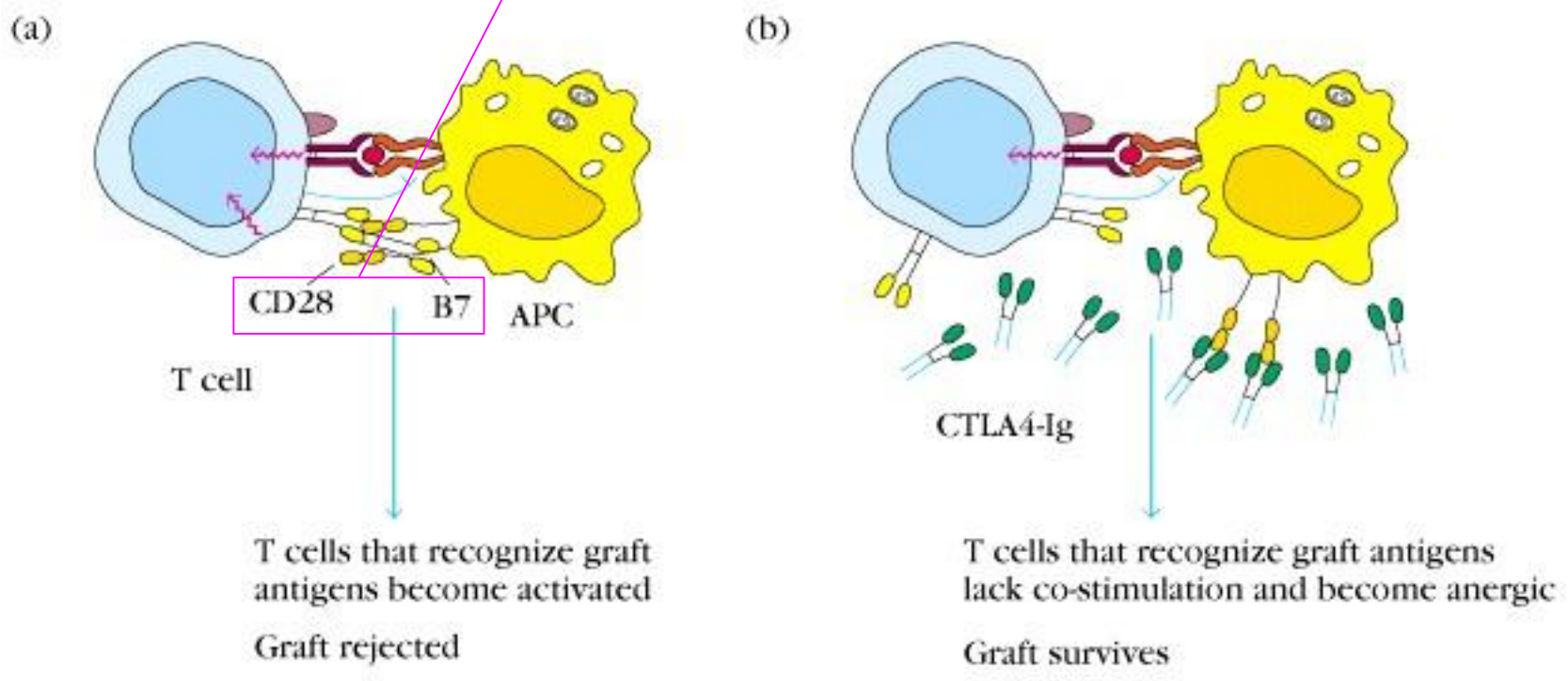


تدل عل أهمية المعالجه بالمثبط المناعي في نجاح الزراعه والبقاء حيا

Specific Immuno-suppression therapy

a) Monoclonal antibodies against T cell components or cytokines

b) Agents blocking co-stimulatory signal "B7 , CD28 "



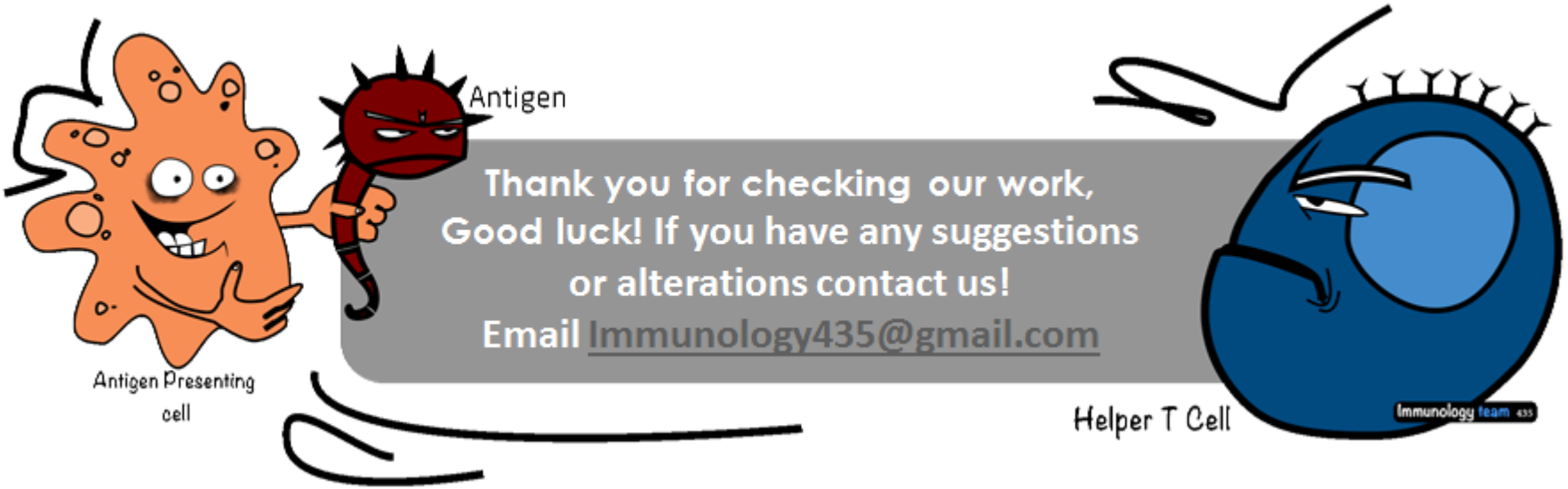
Immuno-suppresive Therapy

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

especially (blood cancer)lymphoma & leukemia

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



Source:
Owen Kuby Immunology book