SIBO
Società Italiana Banche degli Occhi

Azienda Sanitaria Locale
Avezzano Sulmona
L'Aquila

Banca degli Occhi
di L'Aquila
Centro di riferimento regionale
per le donazioni e i trapianti di cornea

Trapianto di cornea: la risposta immunitaria nel rigetto

Azienda Sanitaria Locale
Avezzano, Sulmona,
L'Aquila

CENTRO REGIONALE IMMUNOEMATOLOGIA E TIPIZZAZIONE TISSUTALE
Registro Regionale Donatori Midollo Osseo
Accreditato dall'American Society for Histocompatibility and Immunogenetics (A.S.H.I.) n° 11-9-IT-04-1
Accreditato dall'European Federation for Immunogenetics (E.F.I.) n° 07-IT-024.976
(P.O. "S.Salvatore" – via Lorenzo Natali 67100 - L'Aquila) Tel. +39 0862368236 ; Fax +39 0862 368603
Direttore: dott. Franco Papola

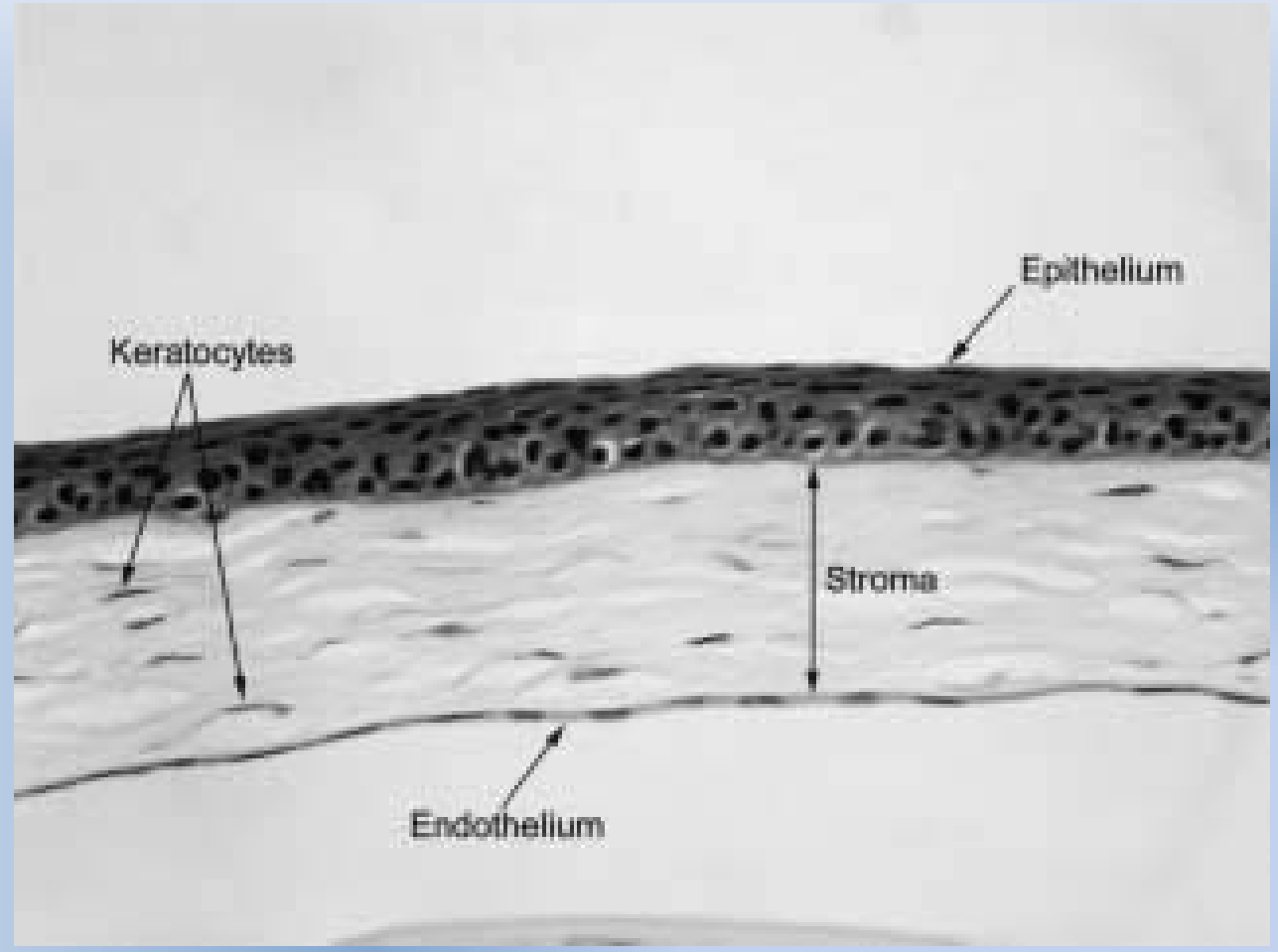

Fig. 3. Histology of the normal cornea. In this photomicrograph the structure of the normal cornea, consisting of an outer layer of epithelium, a middle layer of collagenous stroma with scattered keratocytes, and an inner layer of endothelial cells, is shown (×40 magnification).

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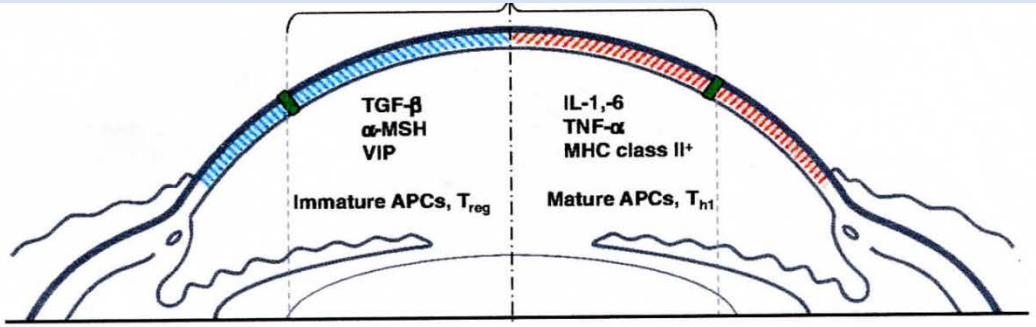


Systemic immune regulation

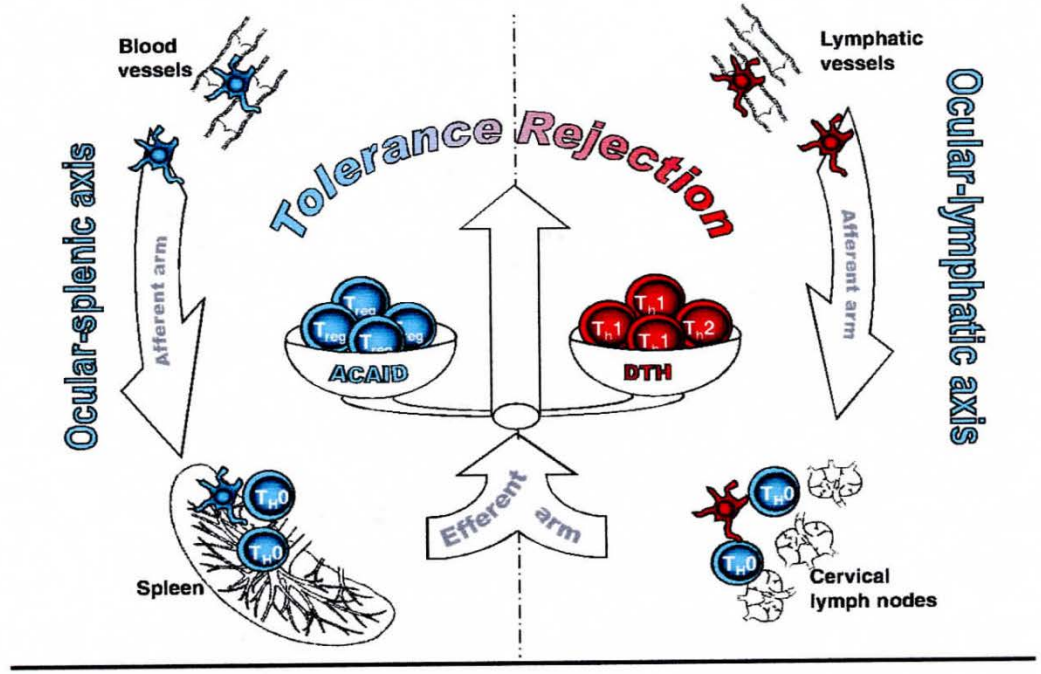


Fig. 1. Local factors contributing to immune privilege (left), and risk factors leading to ablation of corneal privilege (right). α-MSH = α-melanocyte stimulating hormone; ACAID = anterior chamber-associated immune deviation; APCs = antigen-presenting cells; DTH = delayed-type hypersensitivity; FasL = Fas ligand; IL = interleukin; MHC = major histocompatibility complex; TGF-β = tumour growth factor-β; TNF-α = tumour necrosis factor-α; T_{reg} = regulatory T cells; VIP = vasoactive intestinal peptide.

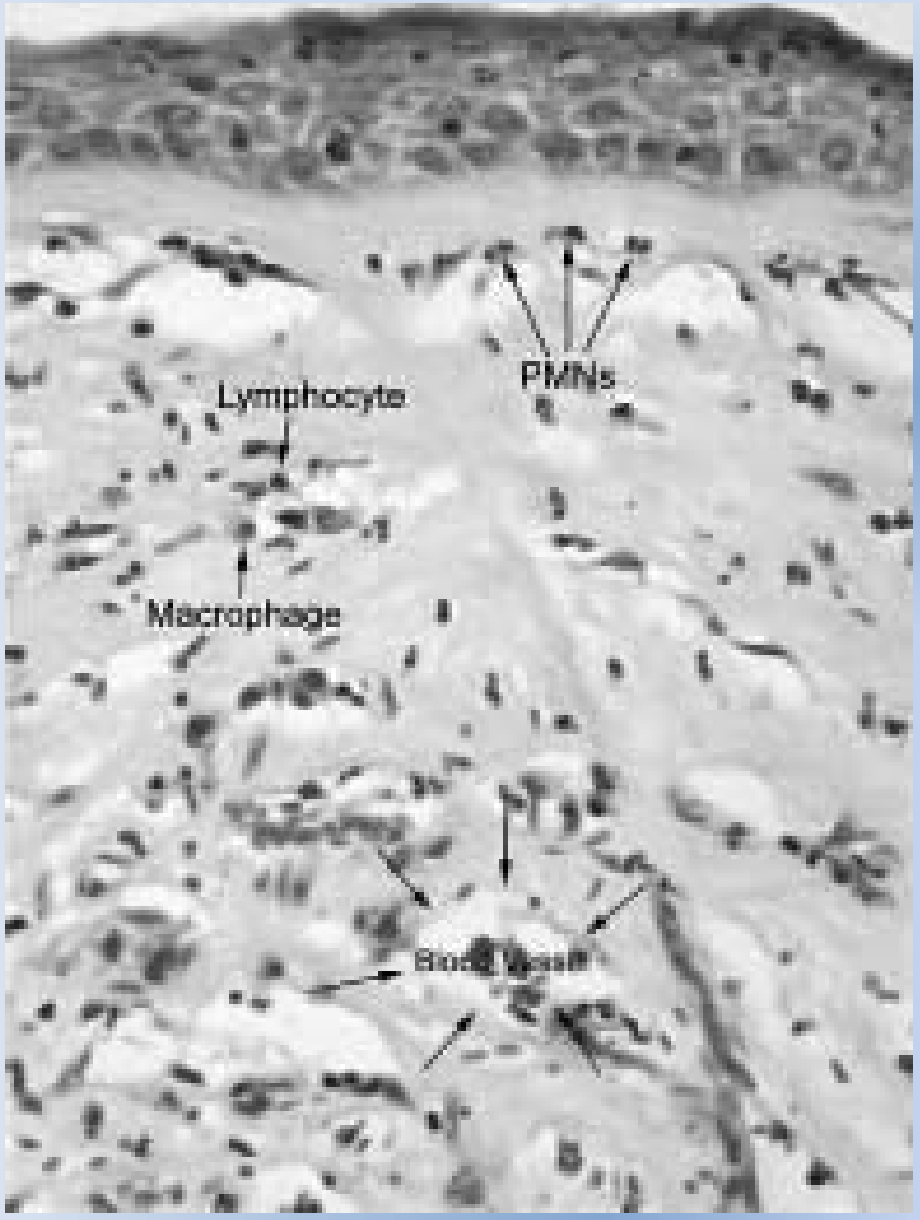
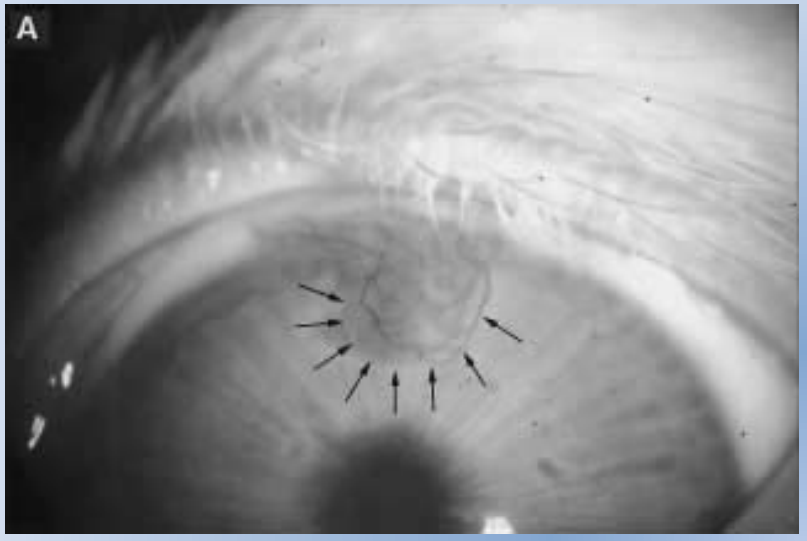


Fig. 2. Histopathology of corneal allograft rejection.
In this photomicrograph of a corneal allograft undergoing rejection, numerous white blood cells of different morphologies can be seen in the stroma and epithelium of the graft. In particular, cells having the morphology of lymphocytes, macrophages, and polymorphonuclear leukocytes can be seen. Blood vessels are present in the corneal stroma (×100 magnification).



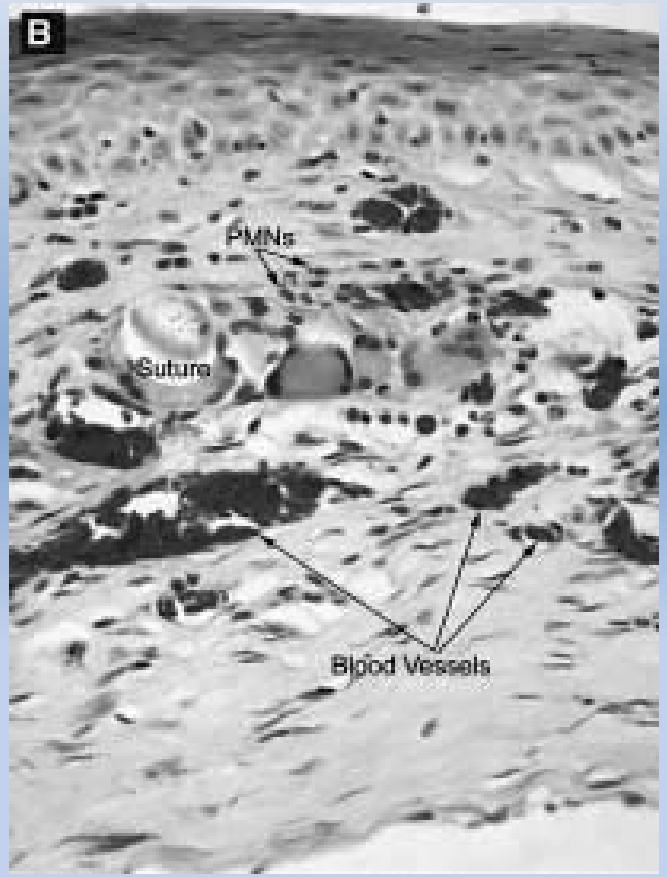


Fig. 4. Neovascularization of the rabbit cornea with silk sutures. (A) Slit lamp photograph of a vascularized cornea shortly after removal of the silk sutures. The dense neovascularization of the cornea in the area where the sutures were placed can be seen (arrows). (B) Photomicrograph showing the histopathology of corneal neovascularization induced by a silk suture. The presence of blood vessels and inflammatory cells in the stroma and disruption of the stromal matrix induced by the suture can be seen (×100 magnification).

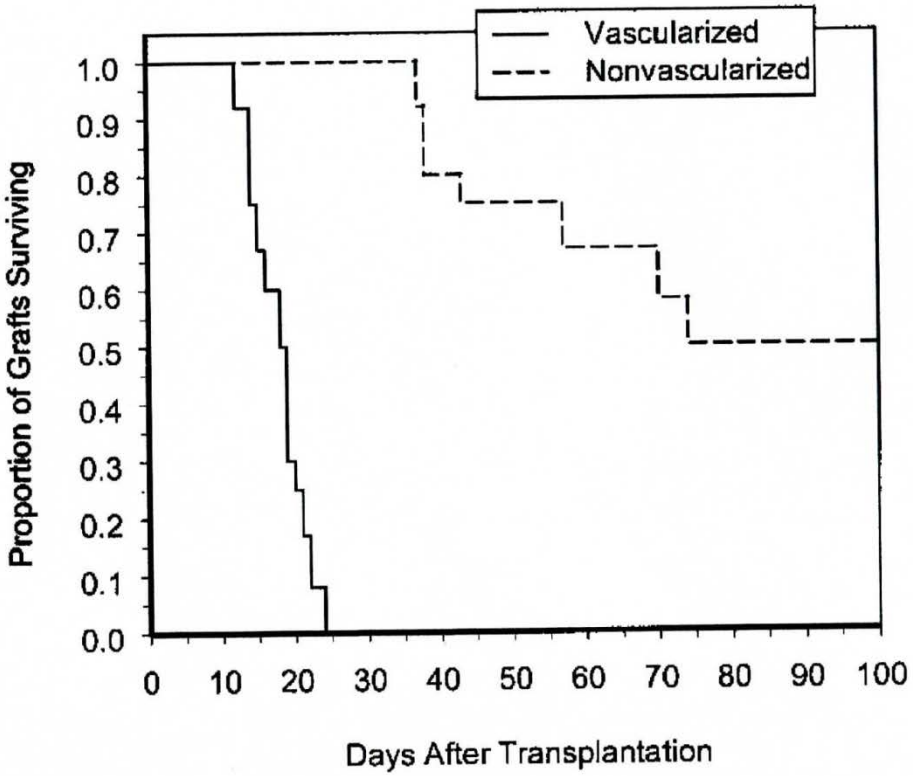


Fig. 5. Kaplan-Meier survival curves showing the difference in survival between corneal allografts placed into vascularized and nonvascularized graft sites in the rabbit eye. Typically 50% or more of corneal allografts placed into nonvascularized graft beds survive for a 100 d observation period, whereas 10% or fewer of corneal allografts placed into vascularized graft sites survive.

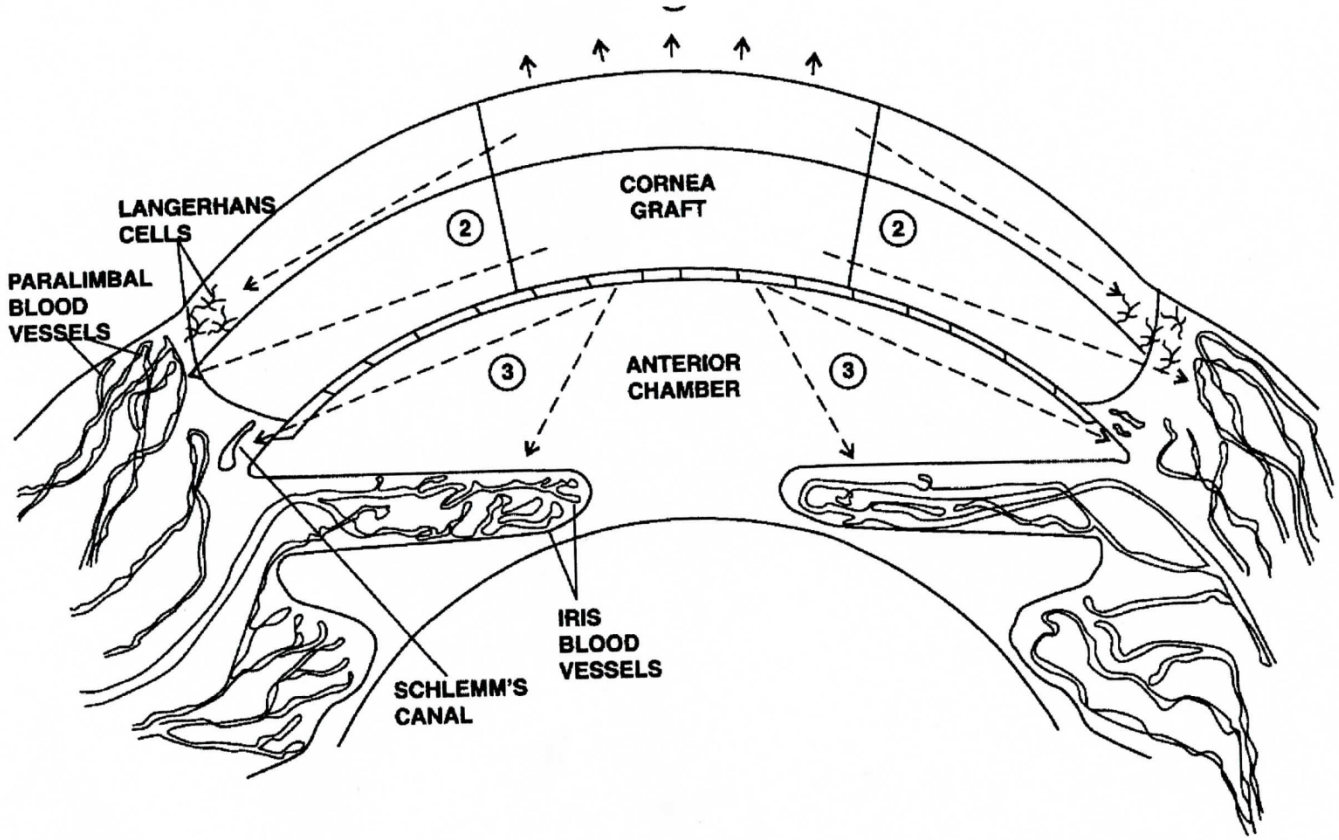


Fig. 8. The possible pathways of passive movement of corneal allograft antigens out of the graft and toward the recipient's immune system is shown schematically. **(1)** Alloantigens exiting the graft into the tears would drain into the tear ducts and be metabolized away without making contact with the immune system. **(2)** Alloantigens diffusing out of the graft laterally through the recipient cornea would reach the paralimbal blood vessels in very small amounts. If these antigens gained access to the blood they would be further diluted in the blood and the amount of alloantigen reaching the lymphoid tissues would be too low to stimulate a response. Similarly, alloantigens reaching the limbus might be taken up by Langerhans cells, but whether or not these cells migrate to the lymphoid tissues and present the antigens is not known. **(3)** Alloantigens diffusing into the anterior chamber might gain entry to the iris blood vessels or, more likely, might exit the eye in the drainage system consisting of the trabecular meshwork and Schlemm's canal. Antigens achieving this route of exit may reach the blood vessels and the lymphoid tissues, but in concentrations too low to stimulate active immunity in the recipient.

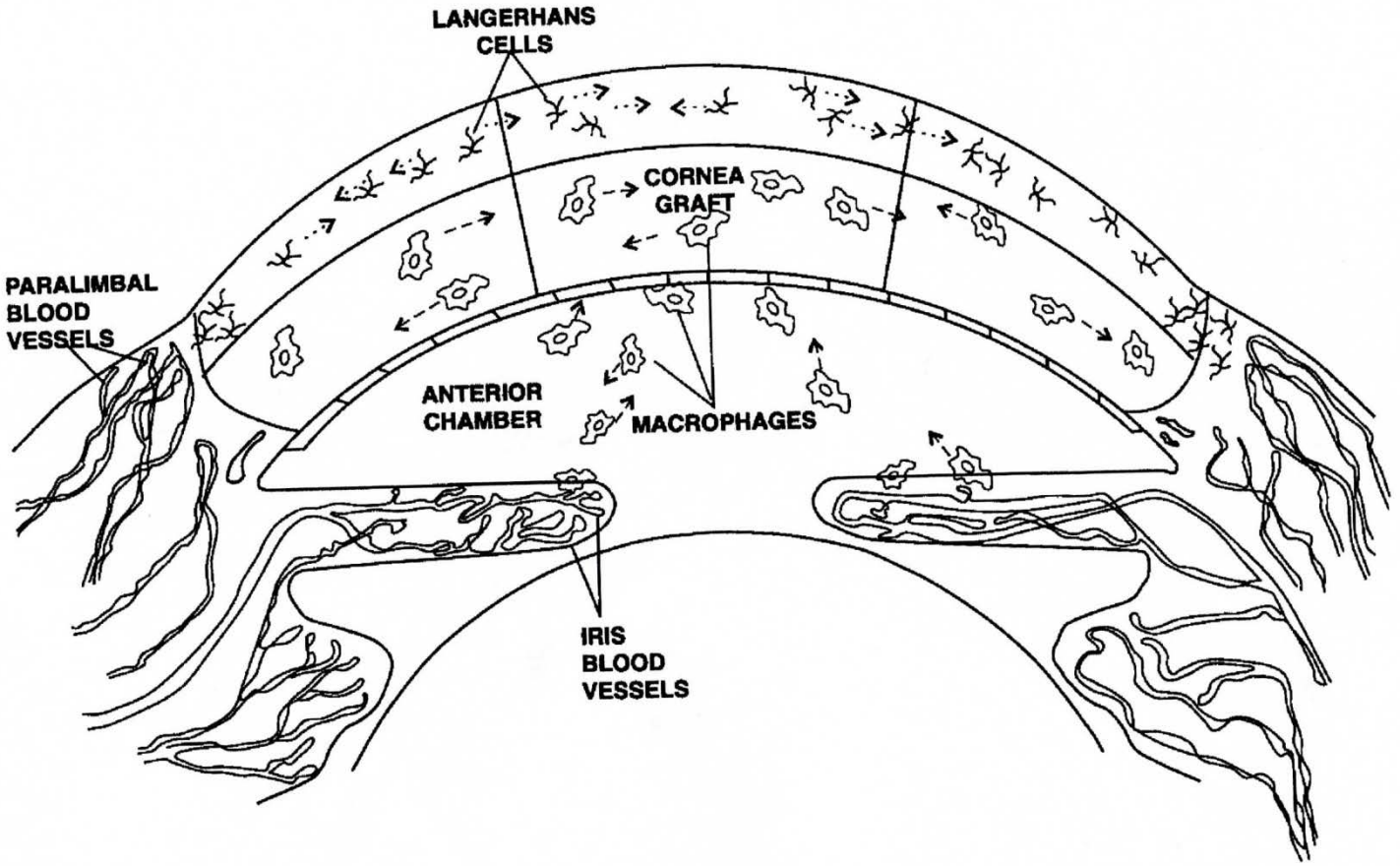


Fig. 9. The process of active transport of corneal allograft antigens from the graft to the recipient's immune system is shown schematically. Langerhans cells in the recipient's epithelium migrate into the graft epithelium and collect donor MHC antigens which are then transported to the recipient's immune lymphoid tissue such as the lymph nodes and spleen. Similarly, macrophages from the paralimbal blood vessels migrate into the graft, phagocytose graft alloantigens, and return to the blood and lymphoid tissues for presentation of antigen to T lymphocytes. A third possibility is shown whereby macrophages might enter the eye from iris blood vessels into the anterior chamber, phagocytose and process graft alloantigens in the anterior chamber or on the corneal graft endothelium, and return with the processed antigens to the iris vessels and the recipient's immune system.

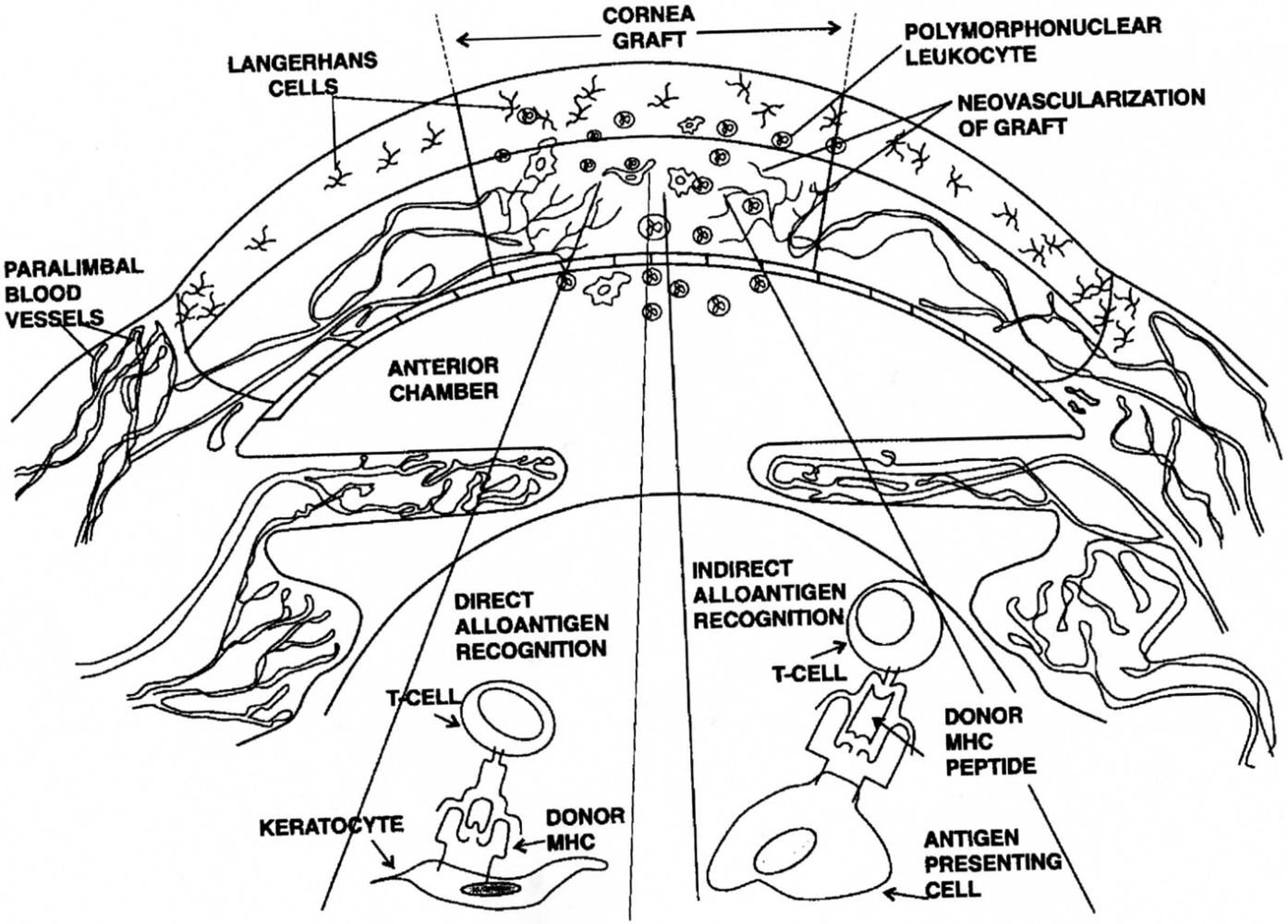
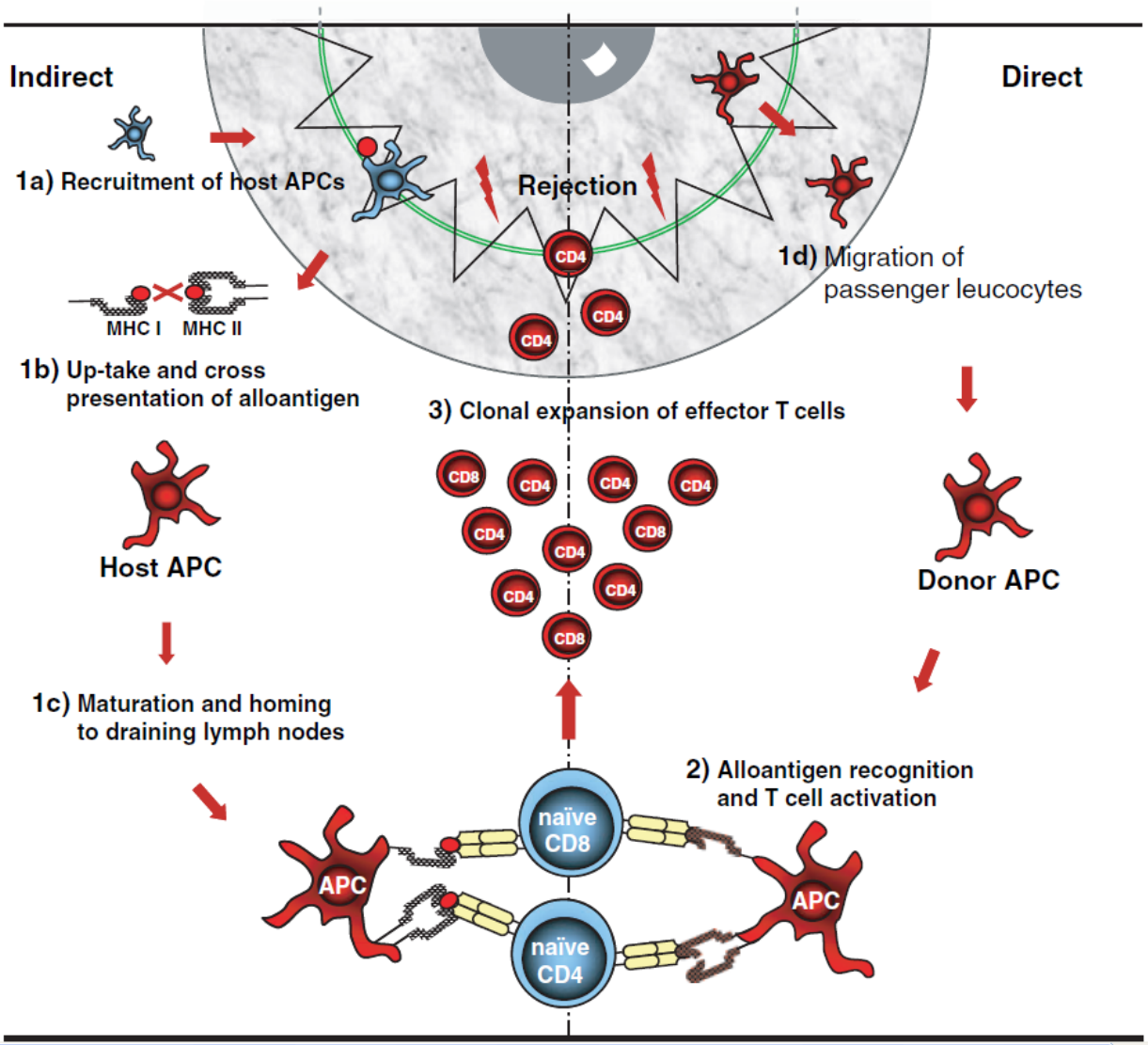
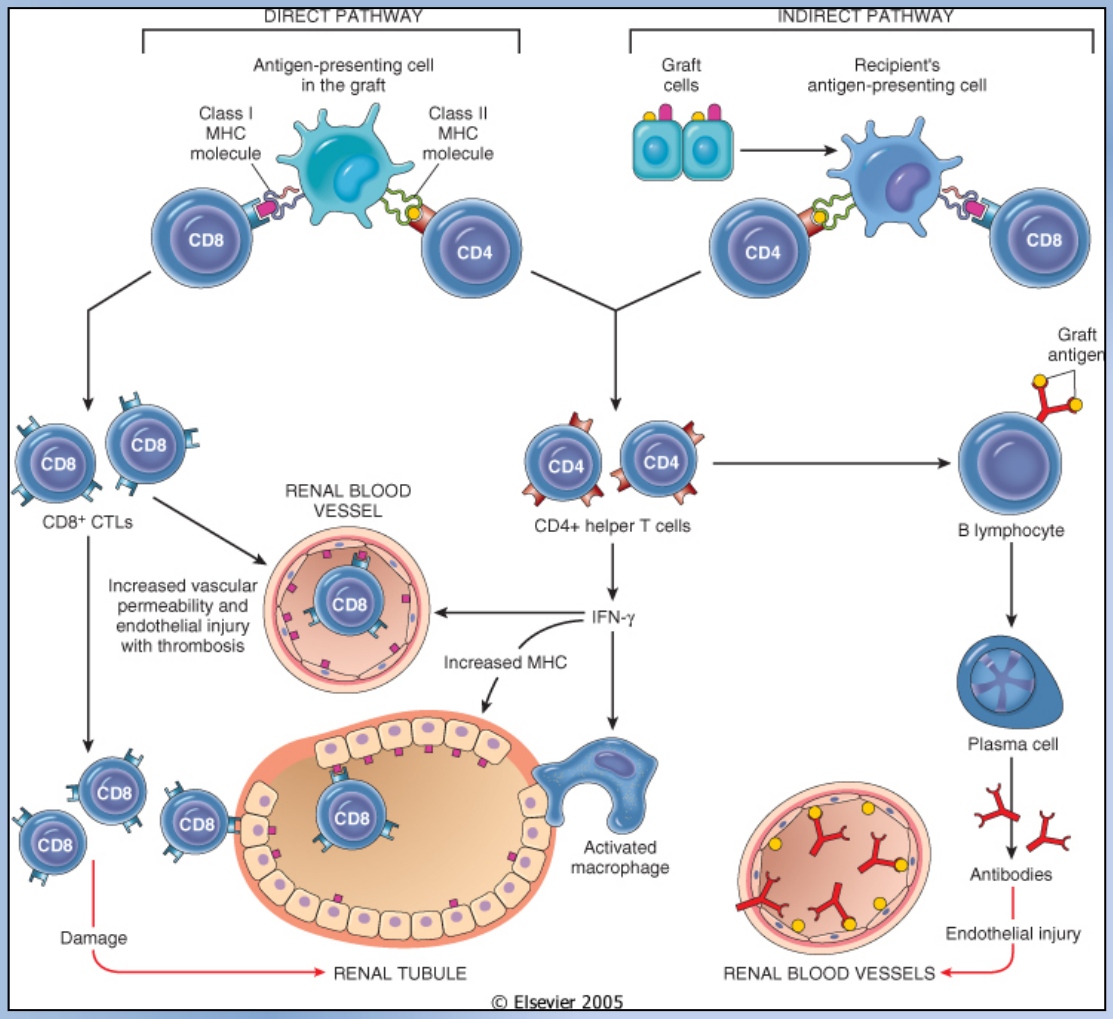


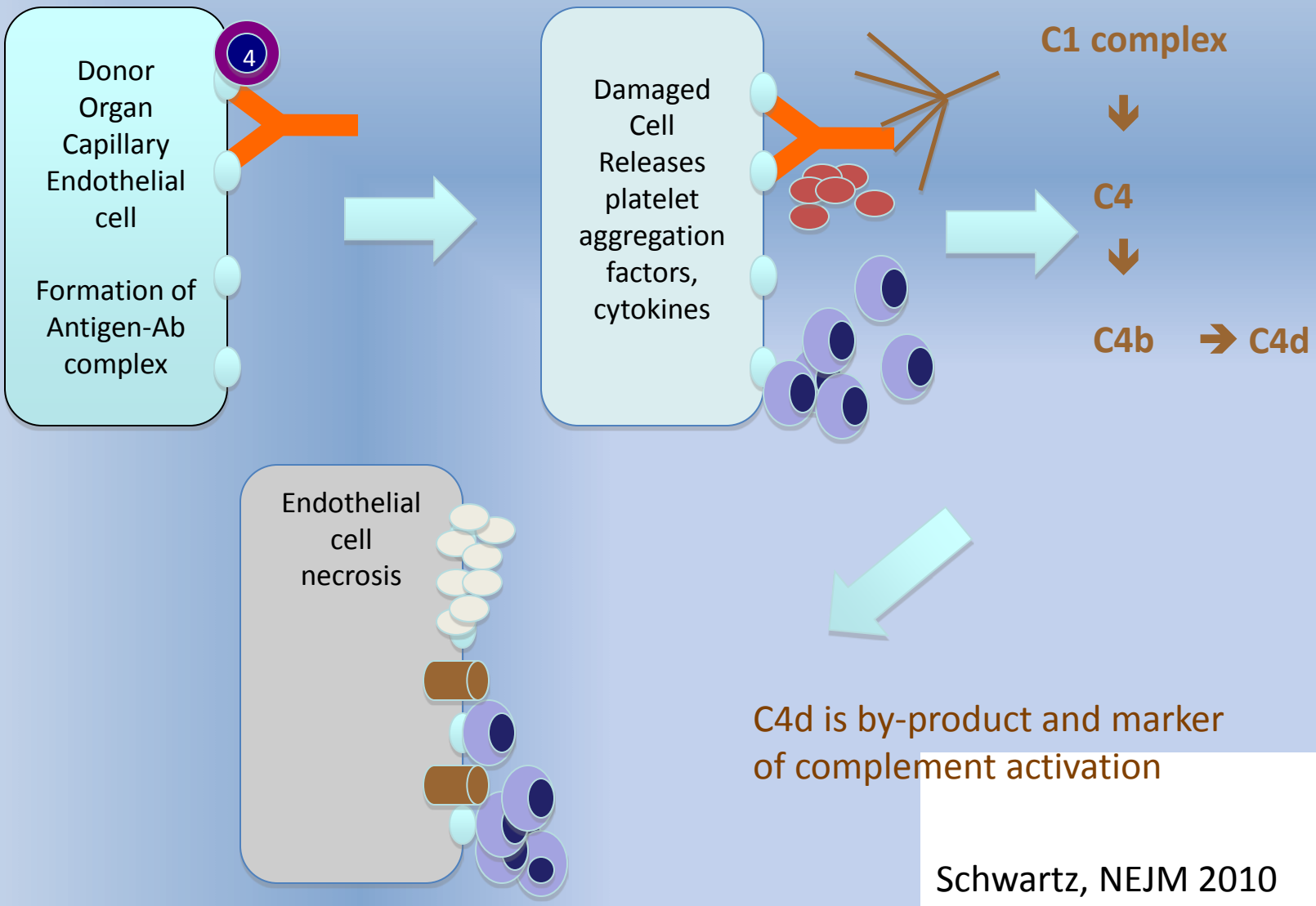
Fig. 10. The complexity of corneal alloantigen recognition and graft rejection is shown schematically. As depicted, direct alloantigen recognition could occur if corneal allograft cells express foreign MHC molecules which are recognized by T lymphocytes migrating into the graft. These T cells would then become activated and direct further immune attack on the graft. Alternatively, in the indirect recognition of alloantigen, antigen-presenting cells migrating into the allograft might process donor MHC antigens and present these antigens to lymphocytes entering the graft. In this instance, the recipient T cells would recognize self MHC and a donor MHC peptide. Direct or indirect alloantigen recognition may also occur outside of the graft in the lymphoid tissues. During rejection additional cells present in the graft include Langerhans



Meccanismi immunologici nel rigetto



Pathophysiology of AMR



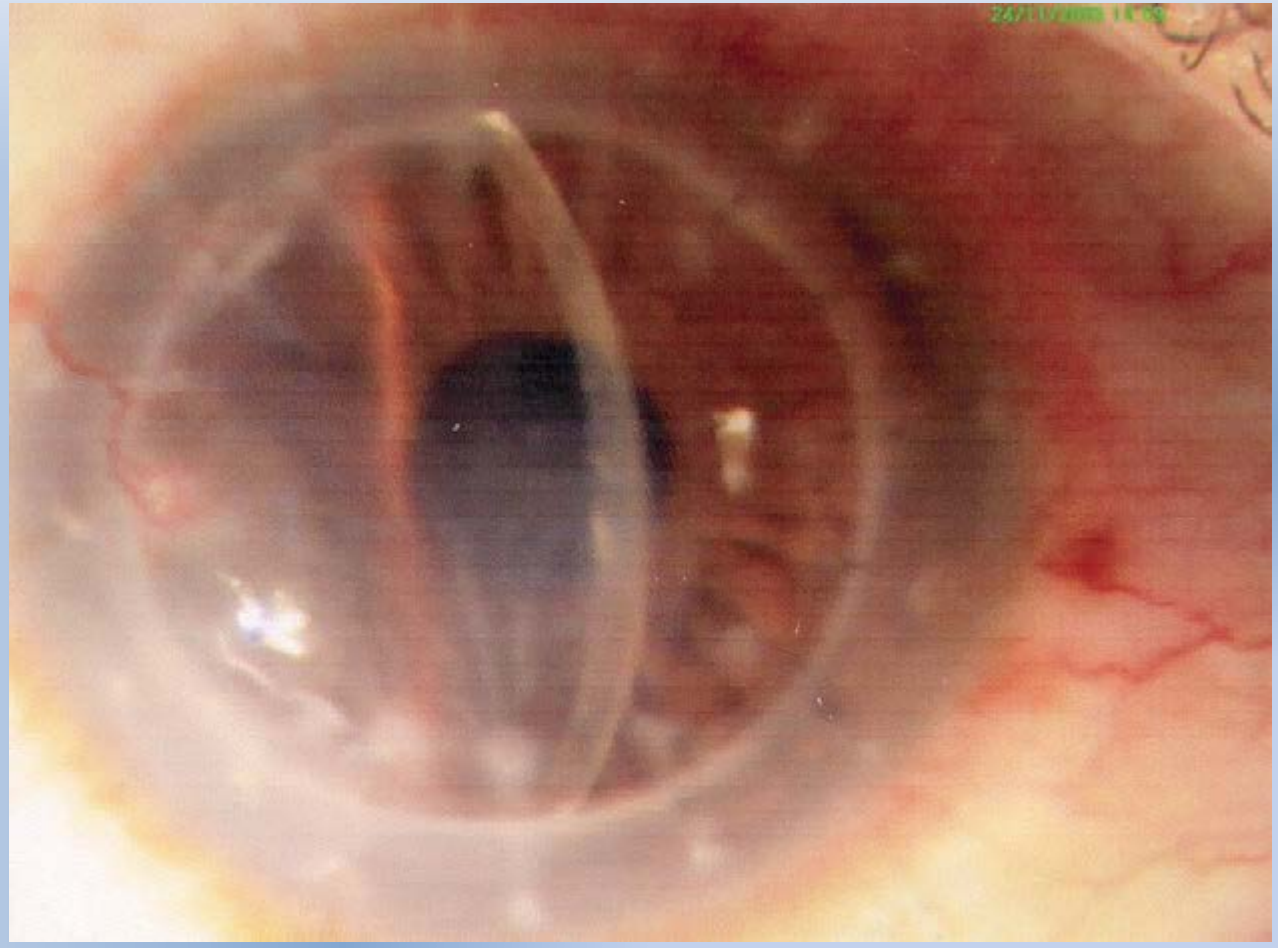
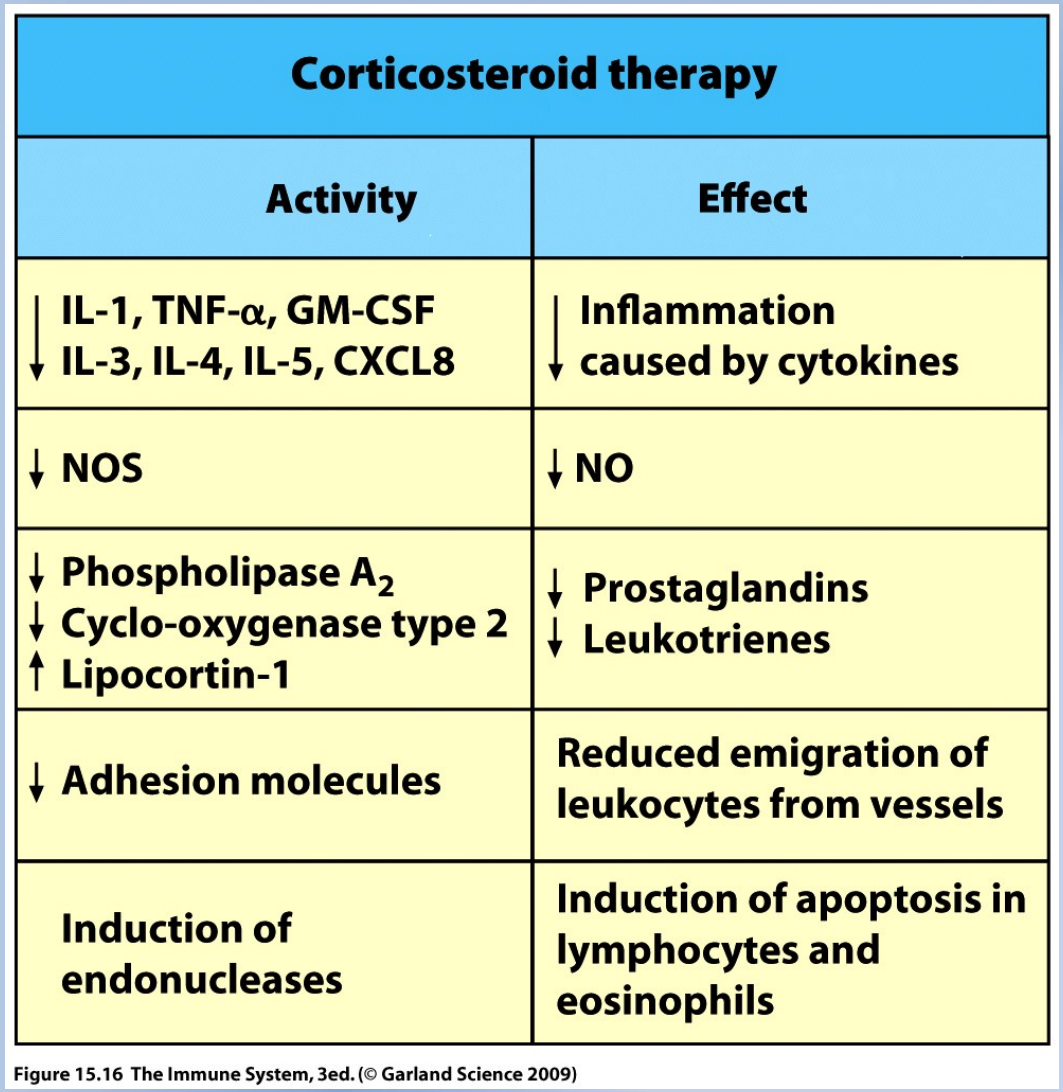


Fig. 1. Combined stromal and endothelial graft rejection showing differential graft edema with stromal haze. (Note the prominent cut suture end with vascularization, which was responsible for the rejection.)

Surv Ophthalmol 52 (4) July--August 2007

Effects of corticosteroids



Corticosteroid therapy	
Activity	**Effect**
↓ IL-1, TNF-α, GM-CSF ↓ IL-3, IL-4, IL-5, CXCL8	↓ Inflammation ↓ caused by cytokines
↓ NOS	↓ NO
↓ Phospholipase A_2 ↓ Cyclo-oxygenase type 2 ↑ Lipocortin-1	↓ Prostaglandins ↓ Leukotrienes
↓ Adhesion molecules	Reduced emigration of leukocytes from vessels
Induction of endonucleases	Induction of apoptosis in lymphocytes and eosinophils

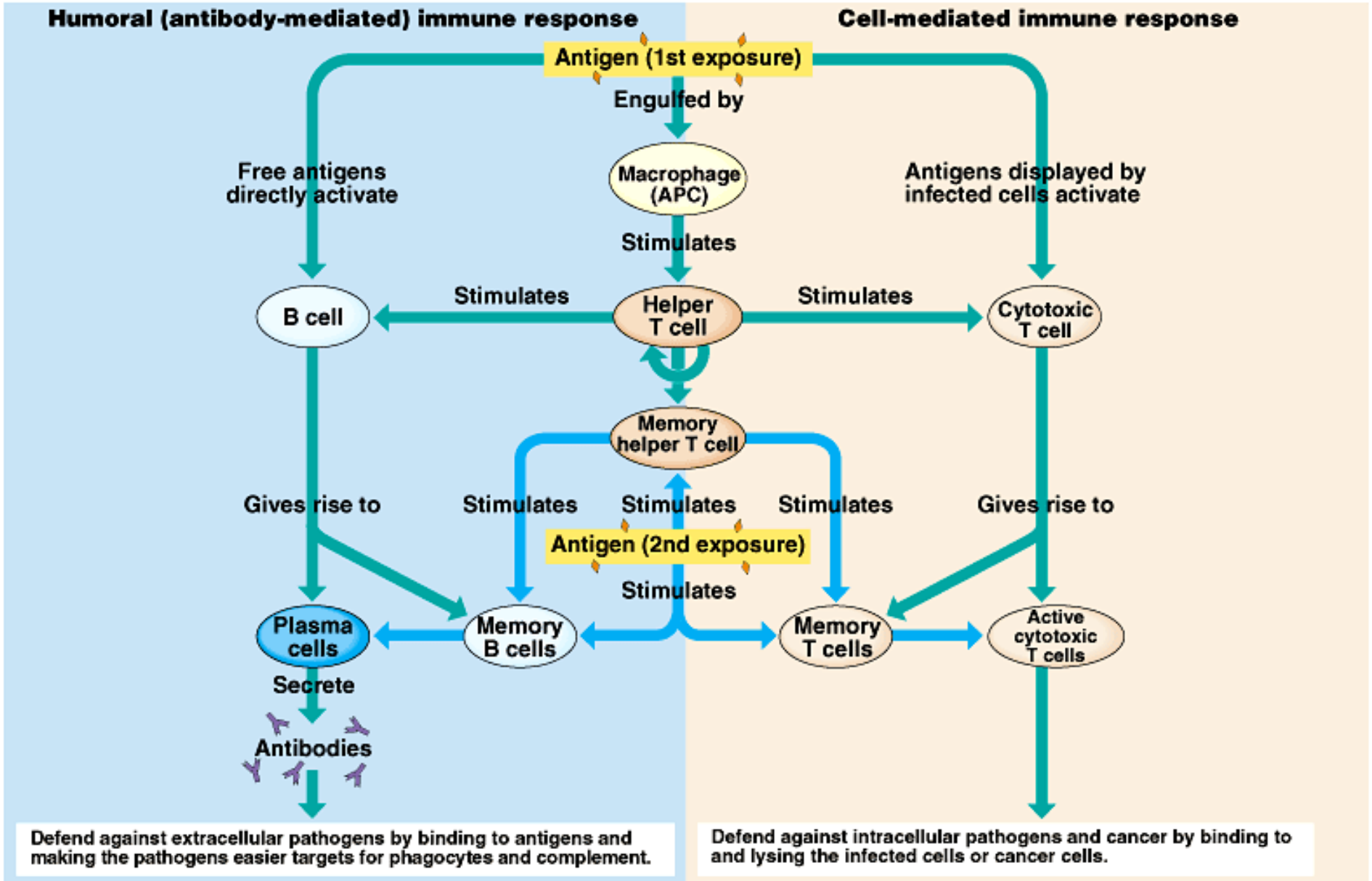
Figure 15.16 The Immune System, 3ed. (© Garland Science 2009)

Cyclosporine A and FK506 inactivate calcineurin (a calcium binding protein), which is required for T, B and granulocyte activation

Cell type	Effects of cyclosporin A and tacrolimus
T lymphocyte	Reduced expression of IL-2, IL-3, IL-4, GM-CSF, TNF-α Reduced cell division because of decreased IL-2 Reduced Ca^{2+}-dependent exocytosis of cytotoxic granules Inhibition of antigen-driven apoptosis
B lymphocyte	Inhibition of cell division because T-cell cytokines are absent Inhibition of antigen-driven cell division Induction of apoptosis after B-cell activation
Granulocyte	Reduced Ca^{2+}-dependent exocytosis of granules

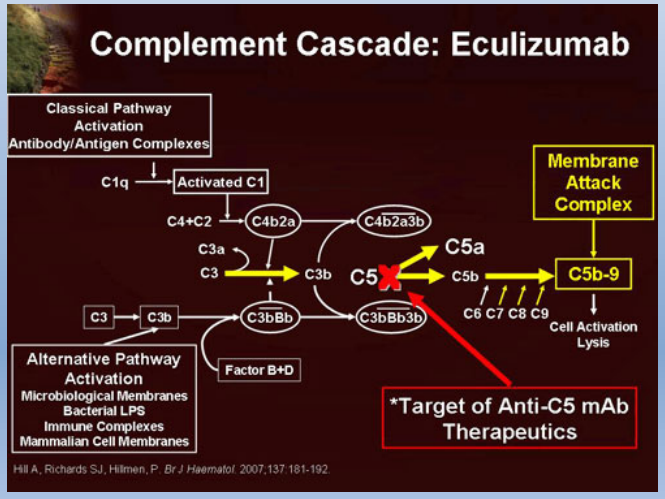
Figure 15.19 The Immune System, 3ed. (© Garland Science 2009)

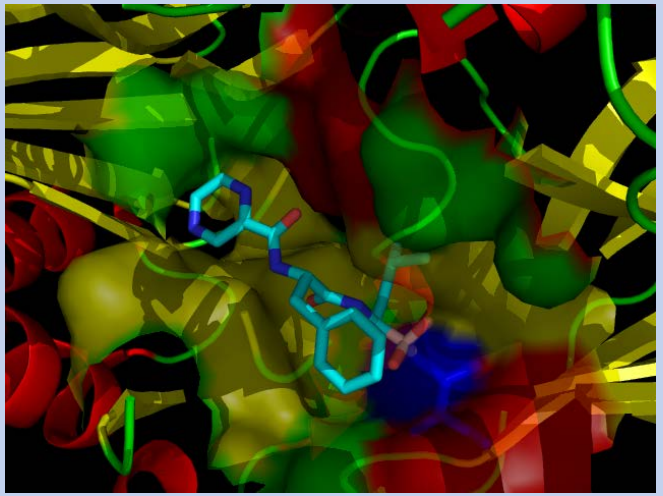
Overview of Immune System Responses



Per agire sulla presenza di anticorpi, abbassare il titolo anticorpale e/o frenare gli effetti degli Ab :

Il **rituximab**, è un farmaco appartenente alla classe degli anticorpi monoclonali; il suo bersaglio è la proteina CD20. Viene utilizzato nel trattamento del Linfoma non Hodgkin delle cellule B, nelle leucemie delle cellule B e in talune malattie autoimmuni.





The boron atom in **bortezomib** binds the catalytic site of the 26S proteasome[4] with high affinity and specificity. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitylated proteins,

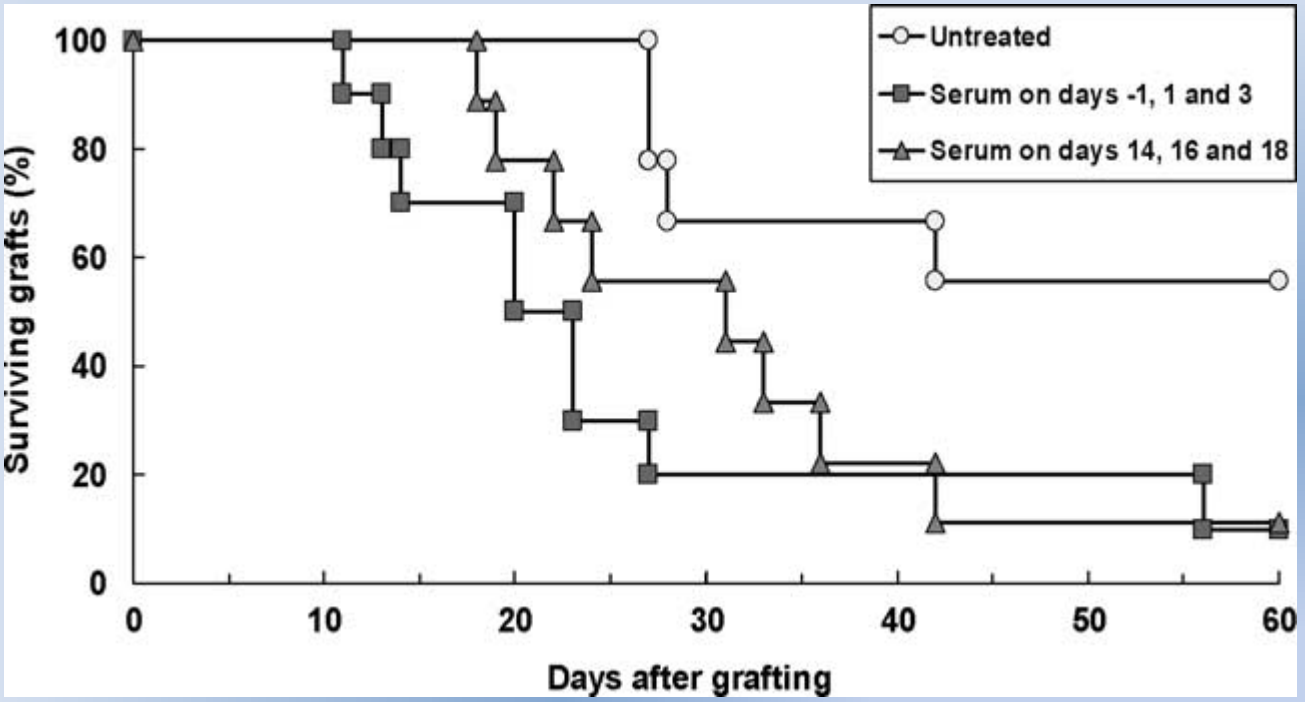


Fig. 1. The effects of passively transfered donor-specific antiserum on surviving of corneal allografts. TheBALB/c recipients of B10 corneal allografts were untreated (9 mice) or were treated with anti-B10 antiserum administered at the period of grafting (10 mice) or at 2 weeks after transplantation (9 mice).

V. Holˊaˇn et al. / Immunology Letters 100 (2005) 211–213

Caso clinico

- Paziente maschio 58 aa
- Nessun evento immunizzante (es. trasfusioni)
- Trapianto cornee dx e sx ca 20 anni prima
- Vascolarizzazione corneale e rigetto
- Perforazione corneale con prolasso dell'iride (descemetocele) e successivo trattamento chirurgico di "ricoprimento congiuntivale"
- Trattamenti locali con corticosteroidi per lunghi periodi di tempo
- Programmazione ritrapianto

Tipizzazione HLA

Ricerca eventuali anticorpi anti HLA

REGIONE ABRUZZO
A.S.L. 1 - Avezzano - Sulmona - L'Aquila

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(P.O. "S. Salvatore" - via Lorenzo Natali 67100 - L'Aquila) Tel. +39 0862 368236 ; Fax. +39 0862 368603
Direttore: dott. Franco Papola

Cognome e Nome: [redacted]

Data di nascita: 30/04/1954

N° di accettazione campione biologico: 12002971

Data di accettazione del campione biologico: 19/09/2012

Data di prelievo: 19/09/2012 Materiale: sangue periferico

RICERCA ANTICORPI ANTI HLA

IgG ANTI HLA CITOMETRIA CLASSE I — LA342B

PRA	NEGATIVA	Metodica:	LUMINEX	Data:	26/09/2012

IgG ANTI HLA CITOMETRIA CLASSE II — LA342C

PRA	51%	Metodica:	LUMINEX	Data:	26/09/2012

SPECIFICITA ANTI HLA IgG CLASSE II — LA257B

Classe II	DR4, DP19, DR16, DRB1*01:02, DP28, DP4 +	Metodica:	LUMINEX	Data:	30/10/2012


HLA Fusion™
Analyze Data Reports Data Sample Patient Info Profile Utilities Help Exit
<<Summary 12002871
Find Ag Sort Ag Excl. Ag DNA CREG - Class II X2 Use Default Graph Raw
DR DR DQA1 DQA1 DQB1 DPA1 DPA1 DPB1
DQ9 DQ8 DQ7 DQ6 DQ5 DQ4 DQ2 DR8 DR12 DR11 DR14 DR13 DR18 DR17 DR10 DR16 DR9 DR7 DR4 DR10 DR103 DR1
DR52 DR52 DR52 DR52 DR52 DR52 DR51 DR51 DR53 DR53 DR53
Statistics
PC: (002) 11669.99
NC: (001) 513.33
PC/NC: 22.734
%A: 12
Cutoff User Current
X2 1000 1063
X4 5000 0
X6 10000 0
X8 15000 0
ResultType: Default
Excluded Antigen
User Cutoff
Donor PRA
Formula Baseline
Comment
Tail Analysis Results
Spec. TP FP TN FN R %I
DR16 2 9 80 0 0.4 10
DR4 3 6 78 2 0.4 60
DP19 1 5 78 0 0.4 10
DP1 1 4 77 1 0.29 50
DP4 1 4 77 1 0.29 50
DP3 1 2 74 2 0.31 33
DP18 1 2 74 2 0.31 33
Epitope Analysis Results
Spec. >= X2 < X2 Mean
DP19 1 0 2449.96
DP1 1 1 2303.56
DR4 3 2 2285.93
DR16 2 0 2106.95
DP4 1 1 2077.85
DP18 1 2 1976.49
DP3 1 2 1690.87
DQ7 1 4 1603.04
Other Assignment
Final Assignment
Spec.
DP19
DP1
DR4
DR16
DP4
DP18
DP3
Remove
Assign -ve
More Tests
Raw Data
Save>>
Confirm>
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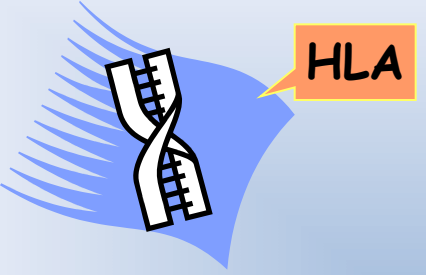


Considerazioni immunologiche e rigetto del trapianto di cornea

In pazienti a rischio di rigetto immunologico

- ✓ 2 o più mismatch HLA classe I
- ✓ 1 o più mismatch HLA classe II

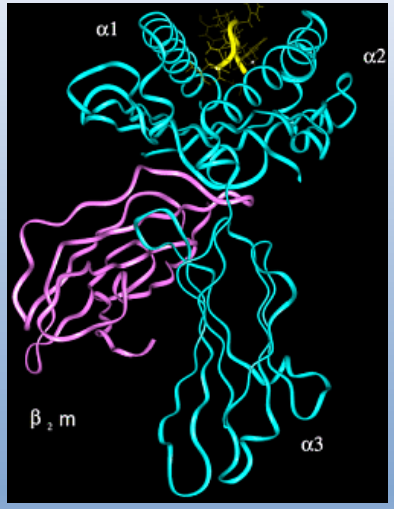
Rischio ↑ 14 volte

✚

- ✓ Anticorpi HLA nel siero (paziente immunizzato)

Rischio ↑ 1000 volte

Come comportarsi nel caso di pazienti ad alto rischio



- **Tipizzare il paziente per gli antigeni HLA di I° e II° classe,**
- **Effettuare lo screening anticorpale per HLA di I° e II° classe,**
- **Evidenziare gli eventuali anticorpi specifici HLA di I° o di II° classe,**
- **Utilizzare cornee che, oltre ad essere compatibili, non posseggono antigeni proibiti (es. DR4, DR16, DR1) in quanto gli anticorpi già presenti avrebbero un effetto sia diretto (rigetto acuto) che favorente la rivascolarizzazione e quindi la perdita precoce della cornea ritrapiantata.**

GRAZIE
per l'attenzione!