

Prevention of corneal graft rejection

Clinical view

Per Montan, MD, PhD

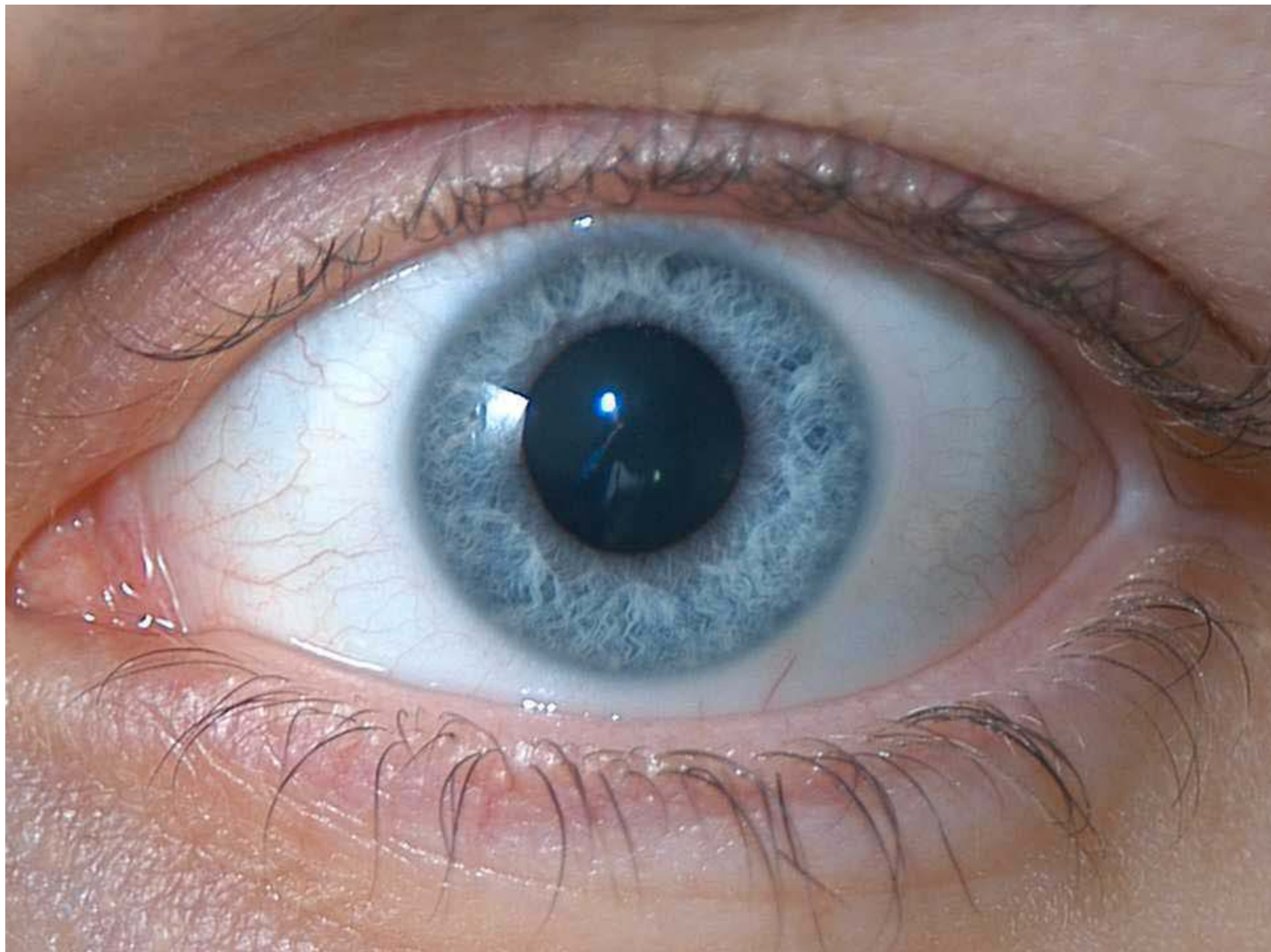
St Erik Eye Hospital, Stockholm, Sweden



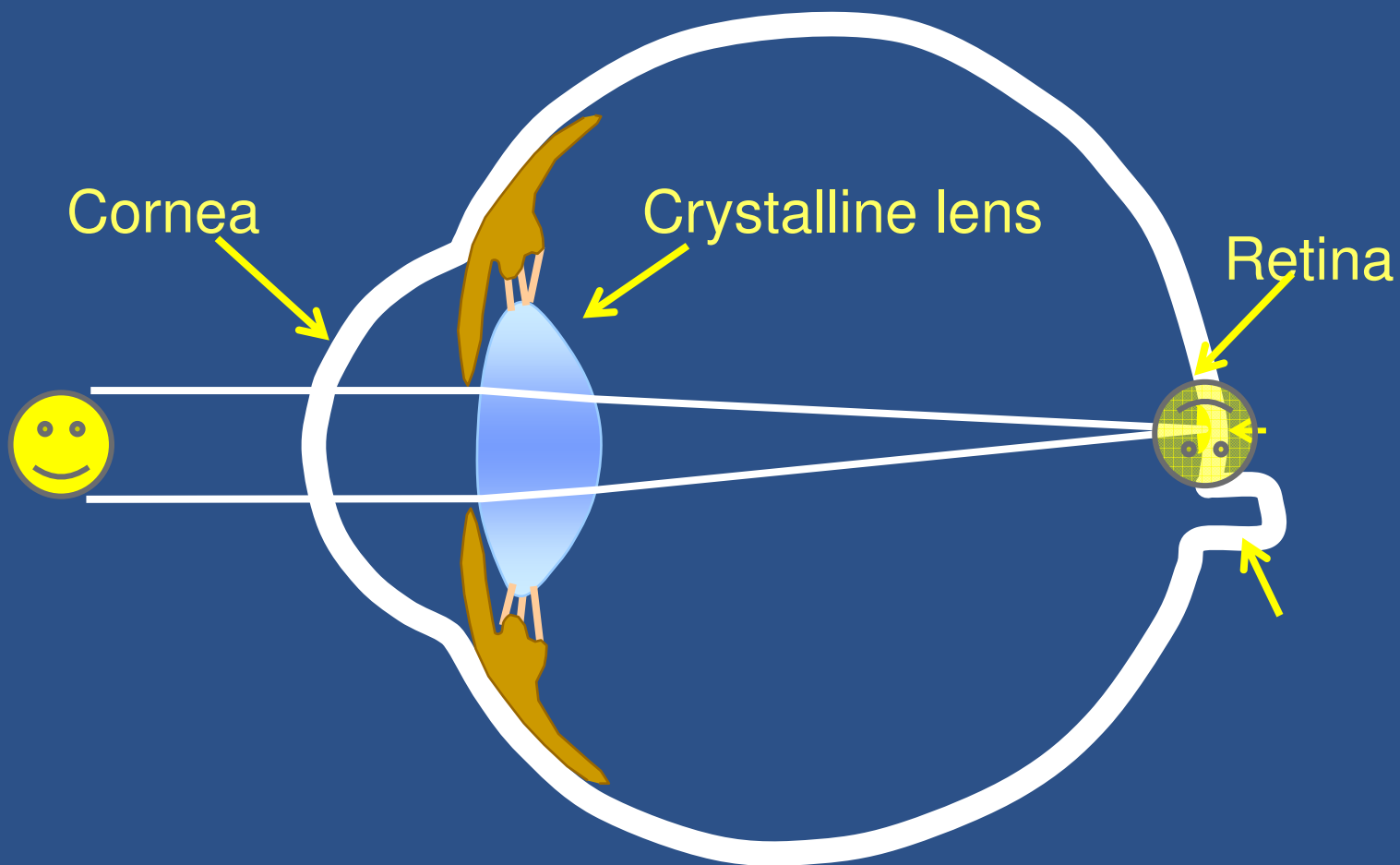
Financial interest?

No!

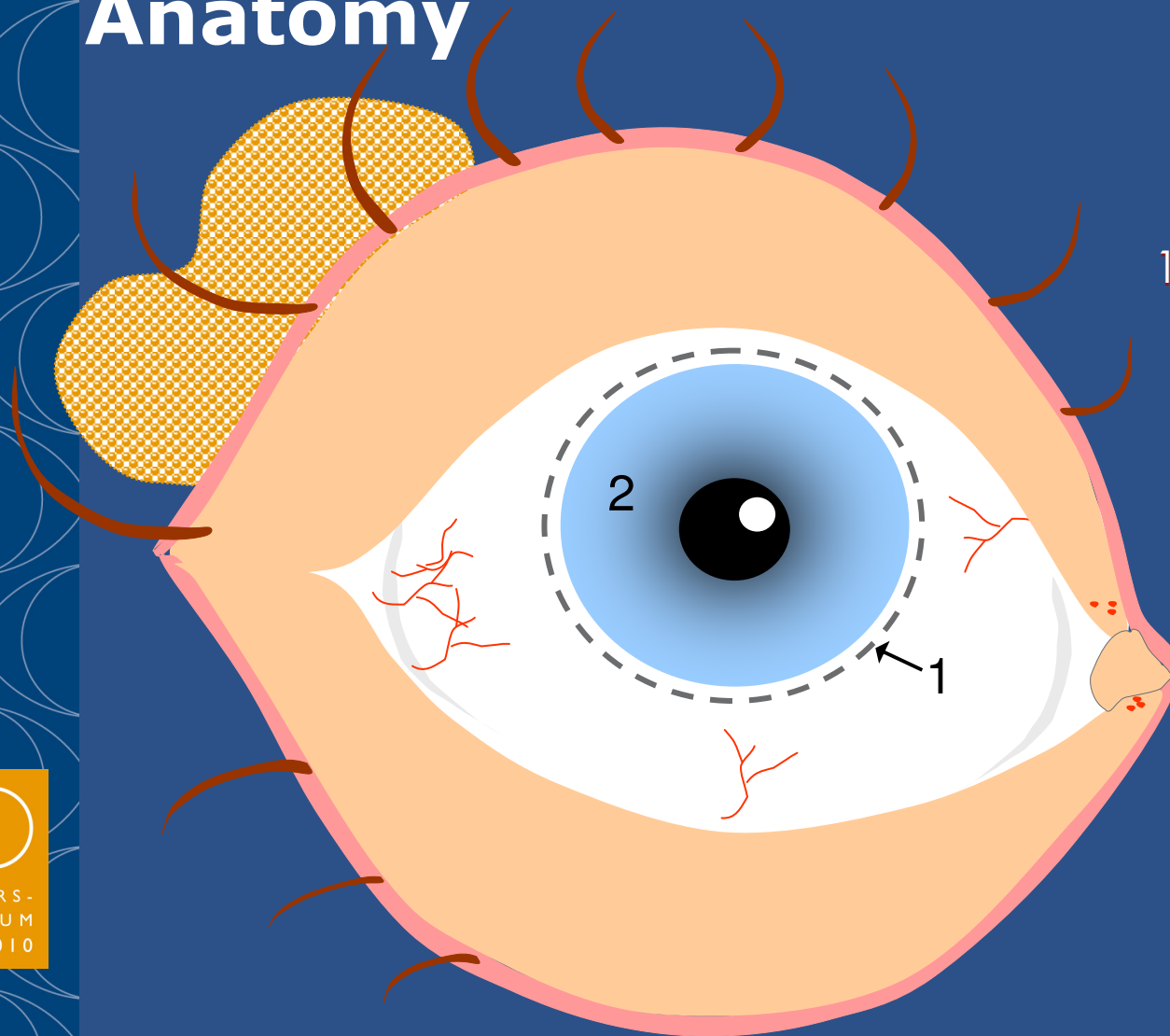




Optics of the eye

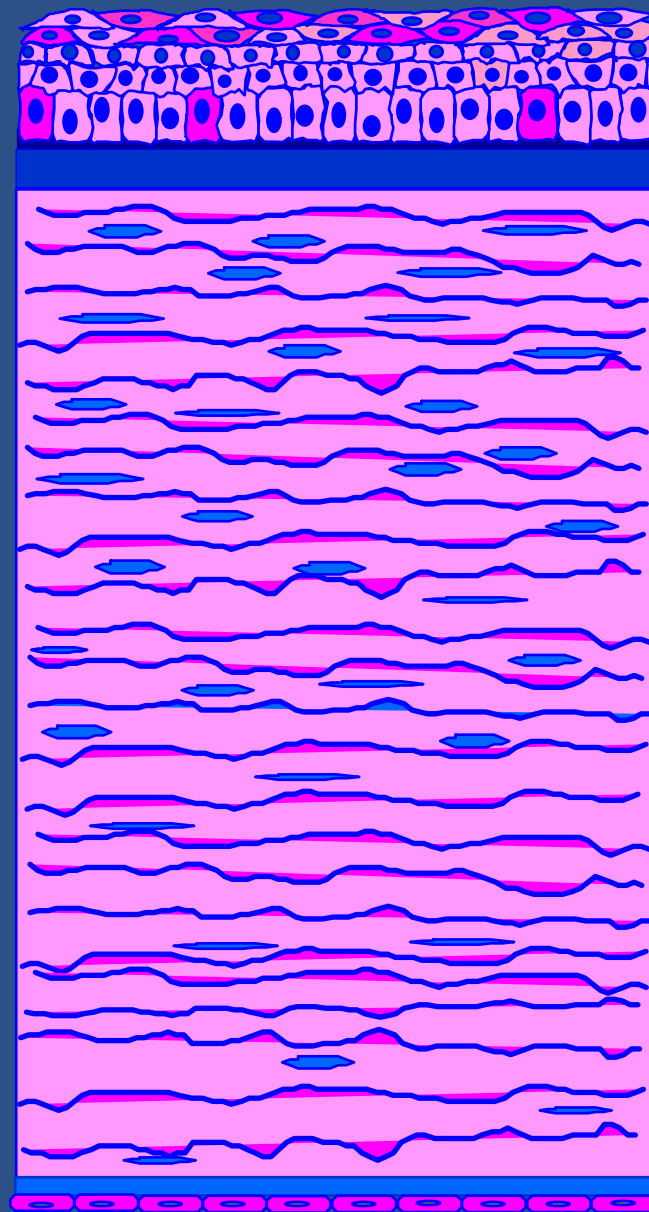


Anatomy



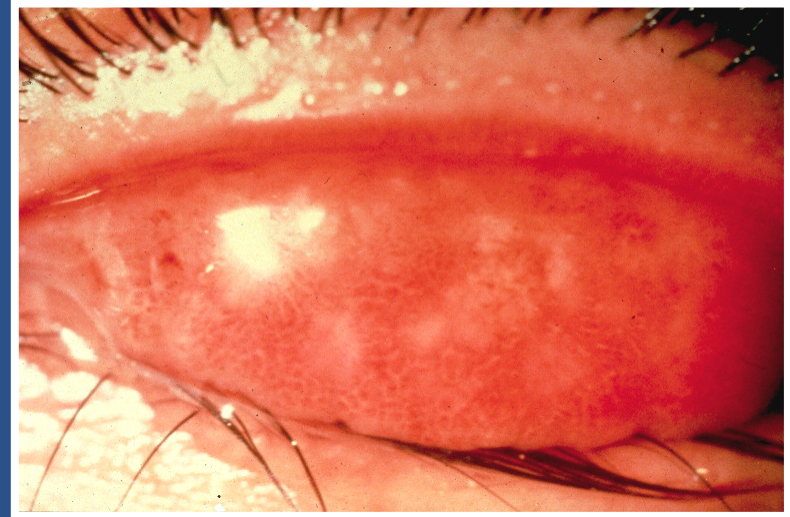
1. Limbal conjunctiva

2. Cornea



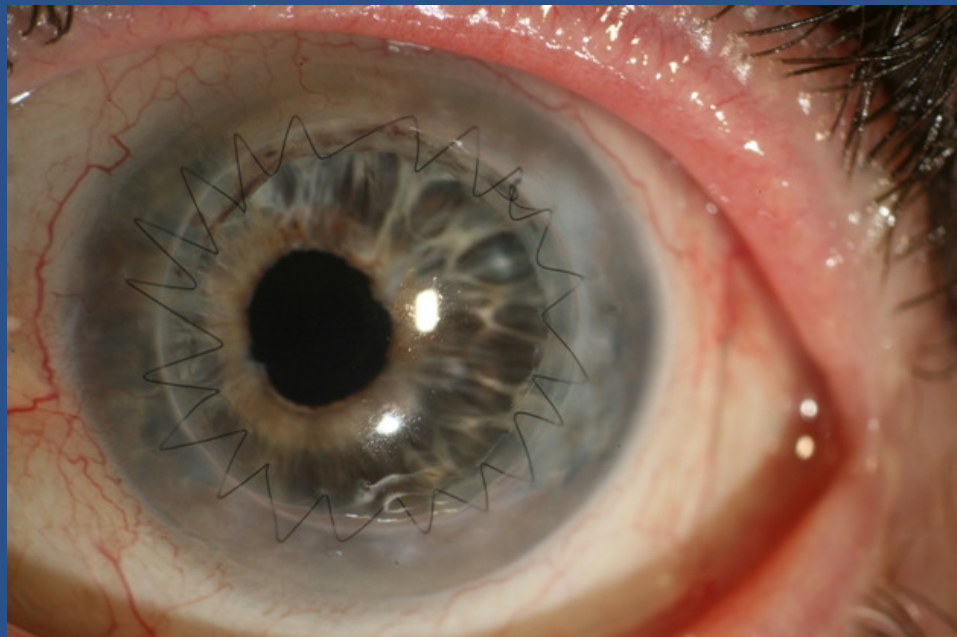
0.5 mm.
Cells
express
HLA I

Trachoma



Aims of keratoplasty

- Restore a clear visual axis.
- Achieve 20/40 or better VA
65% do at 2 yrs (**Br J Ophthalmol** 2002;86:
174 - 80)

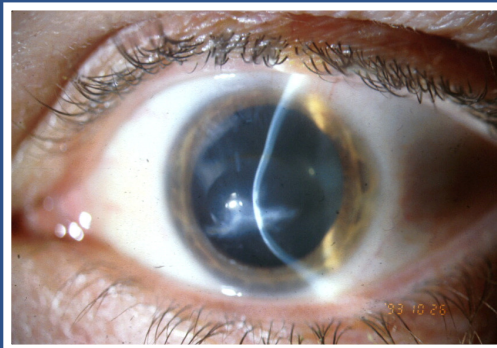


Reasons for keratoplasty 1

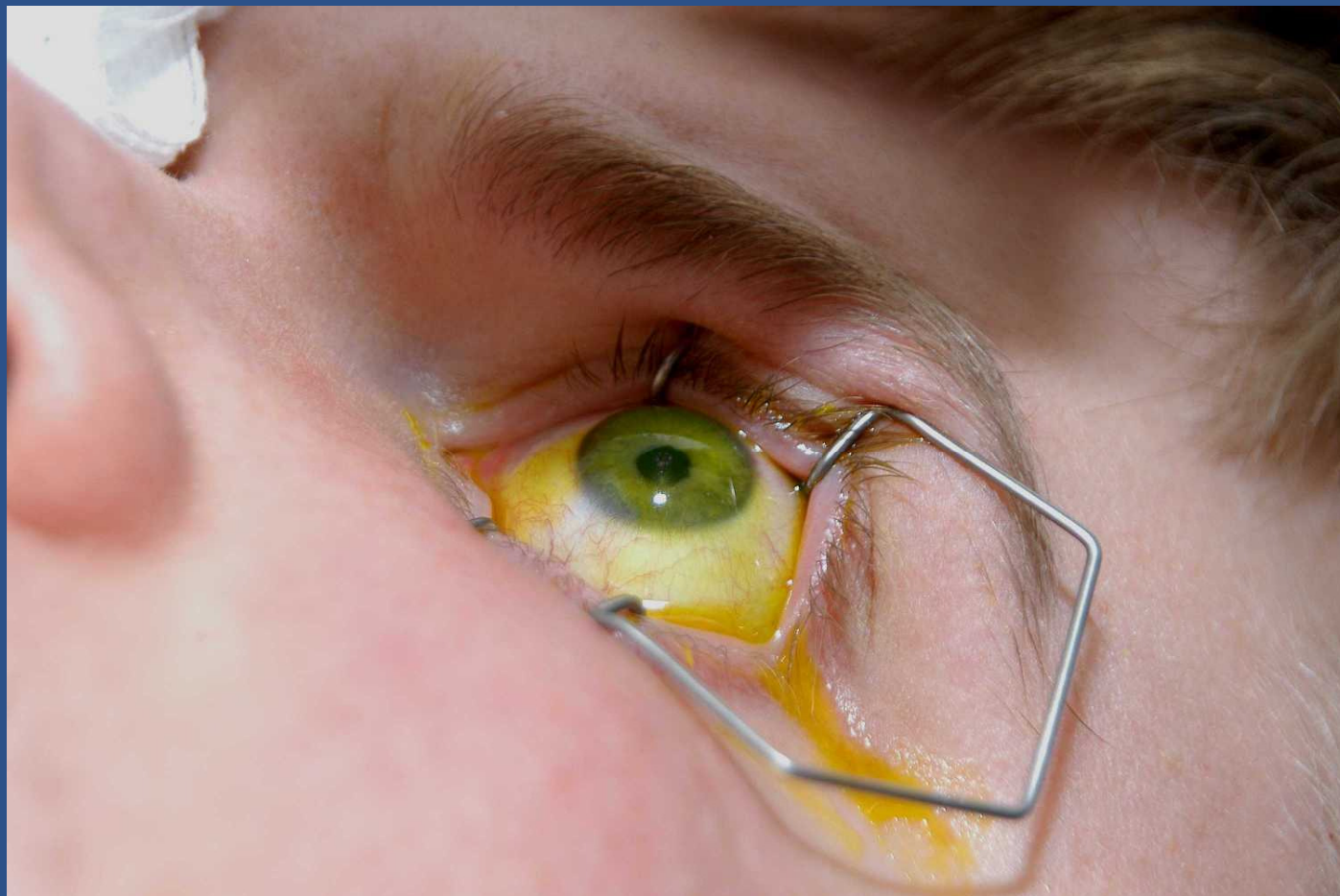
Endothelial failure – INCREASING!!!



Keratoconus - DECREASING?

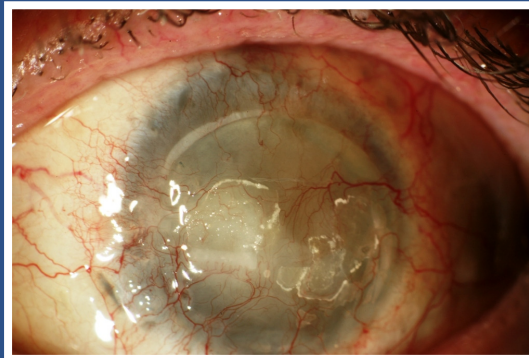


Corneal cross-linking - halting keratoconus?

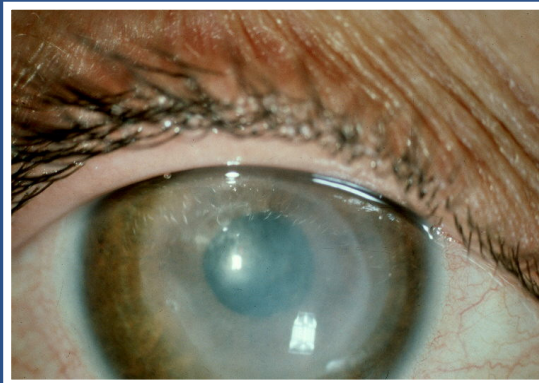


Reasons for keratoplasty 2

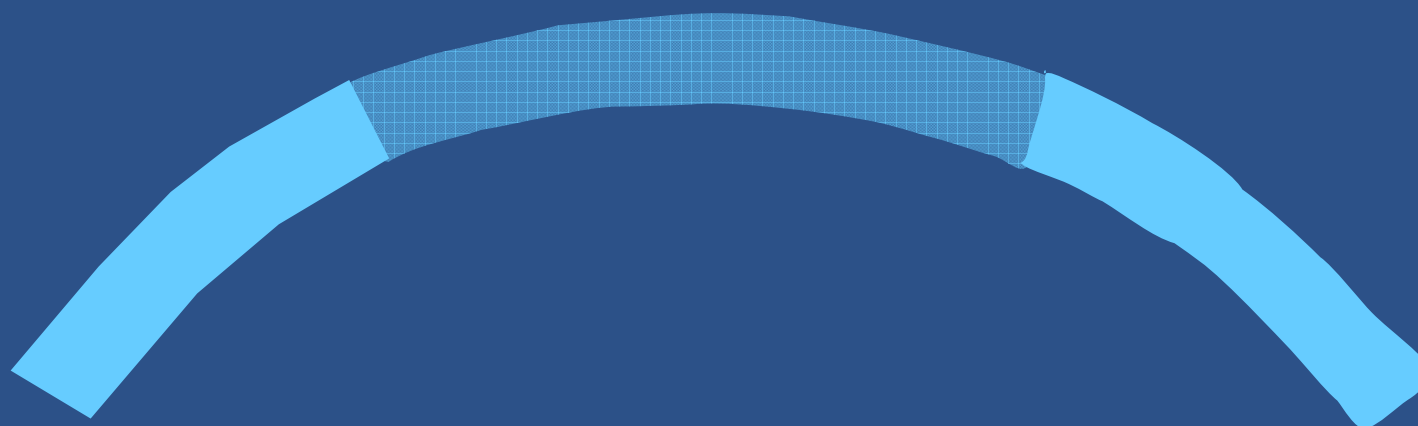
- Regrafts - INCREASING



- Scar (following infection, trauma)

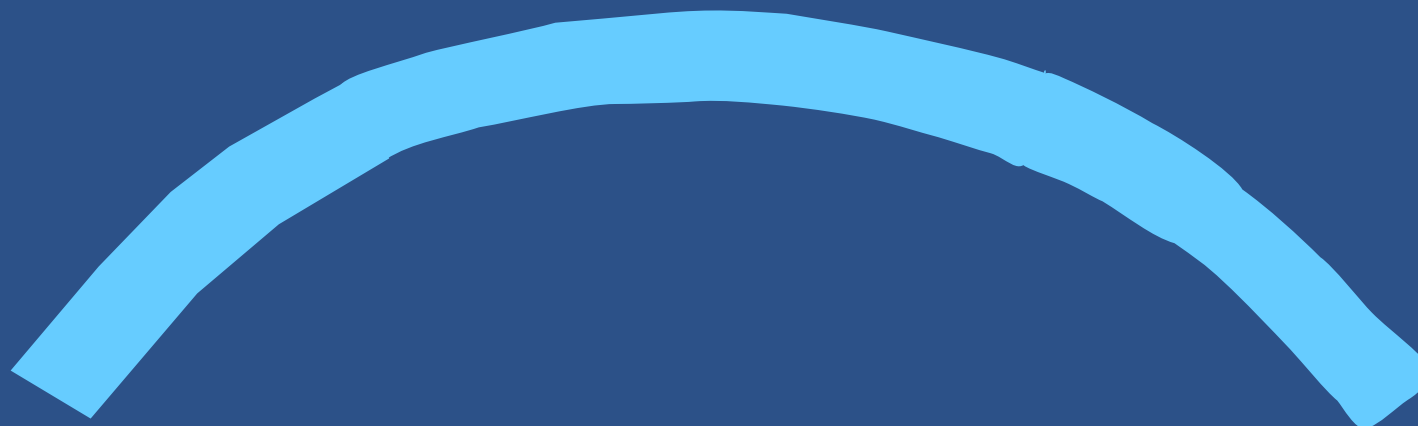


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Traditional penetrating keratoplasty (PK)



Estimated frequency of keratoplasties, Europe

- EEBA statistics 2008
4 in 100 000
- Swedish Cornea Registry 2010
6 in 100 000
- Waiting for an operation in Sweden
6 in 100 000
- US frequency
10 in 100 000



Success = a clear graft

	1 yr	5 yr	10 yr
Kidney ¹	91%	89%	79%
Cornea ²	93%	86%	70%

Notes:

1. Adult first renal transplant 1999-2001
2. First penetrating keratoplasty



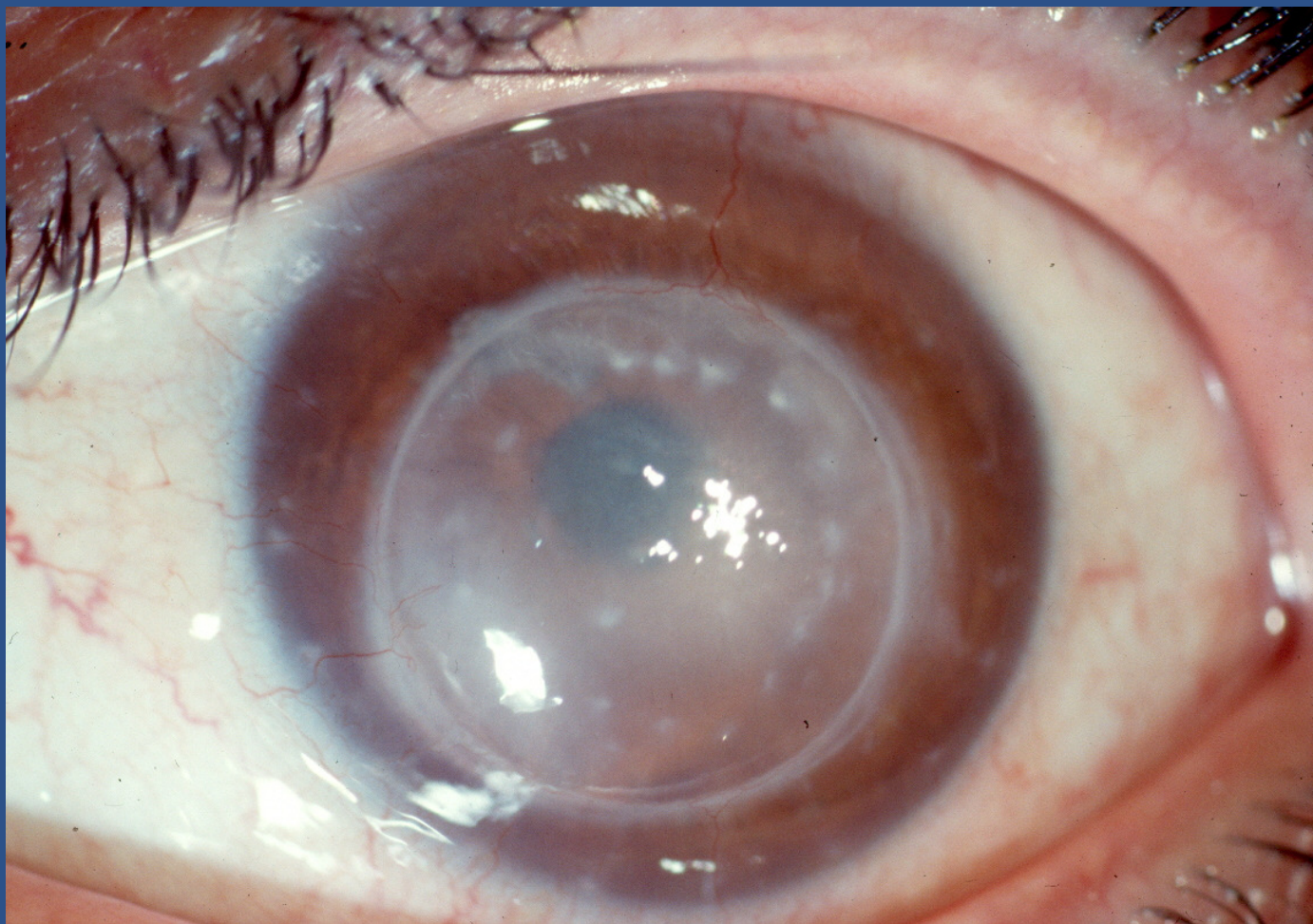
(Data from UK Transplant Activity Report, August 2007)

Decay of endothelial cells and rejection

	1 yr	5 yr	10 yr
None	90%	81%	71%
≥1 episode	72%	49%	34%

(Data from Australian Corneal Graft Registry Report, 2007)

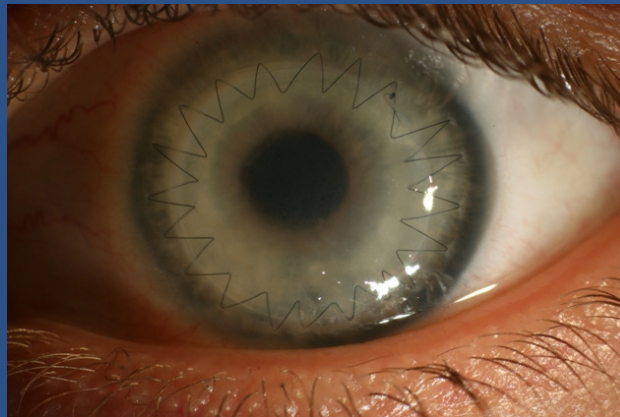
Rejection major threat to transplant survival!!



"Immune privilege" – a misconception

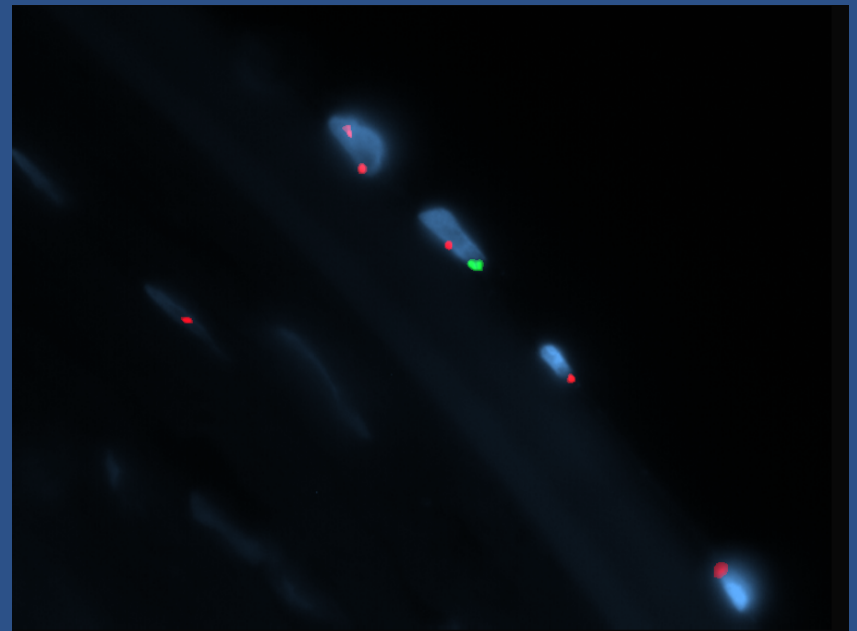
- Keratoplasty induces:
APC activity (Langerhans and
macrophages)
Clonal expansion of CD4⁺ T cells
Lymph- and hemangiogenesis

15% rejection (usually reversible) at 2
yrs.



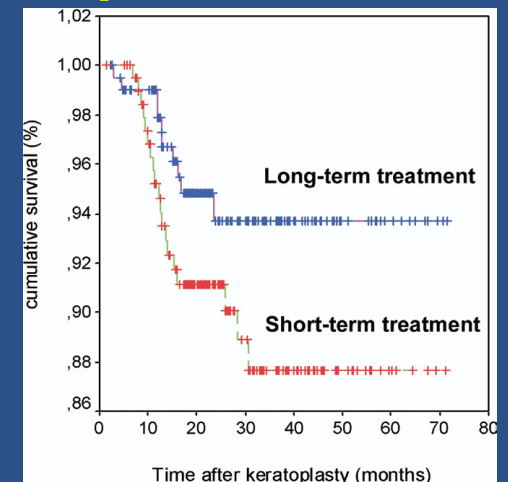
Cellular origin in full thickness transplants

- Mixture of donor and recipient cells for > 10 yrs post-op (iovs. 2009 ;50:2673-8)



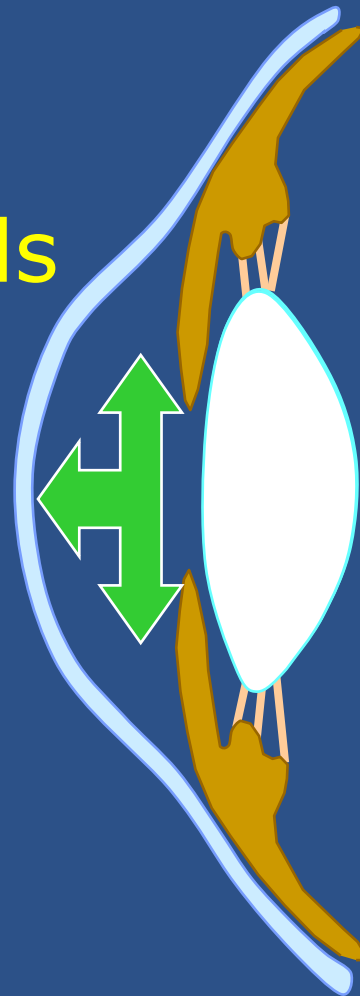
Topical steroids – backbone of R_x

- Dexamethasone or prednisolone 7 – 12 months. Lack of RCTs!!!!
- The best regime NOT defined (12 vs. 6 months better, (**Am J Ophthalmol** 2007; 144:318 – 19)



- Value of contd. low-dose R_x?

Topical steroids



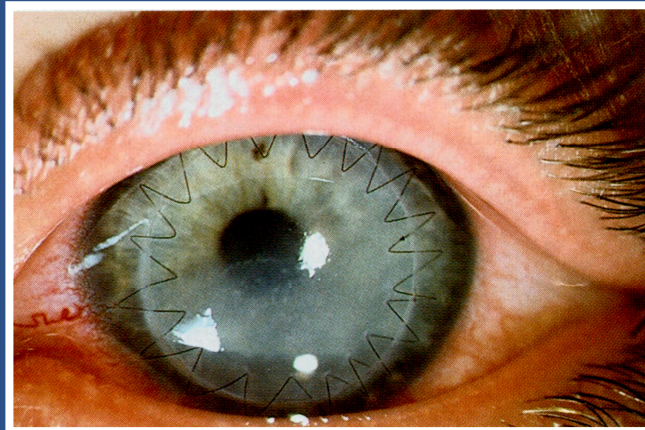
Risk factors for rejection

- Indication (prev. trauma, infection, iatrogenic endothelial failure, **regraft**)
- Co-morbidity (glaucoma, infl disease)
- Vascularised recipient bed
- Young age of recipient (pediatric keratoplasty)
- **PREVIOUS REJECTION**
- **% of high-risk grafts among operated?**



How to deal with high-risk grafting!

- HLA Class I or II matching?
- Systemic immunosuppression?
- Add-on topical R_x?



Tissue matching

- Contradictory results.
- HLA Class I matching - beneficial
- HLA Class II matching – even detrimental?
- 3% of EEBA corneal grafts are tissue matched
- 5 year on-going study in the UK – enrolling 1200 pts *at risk*



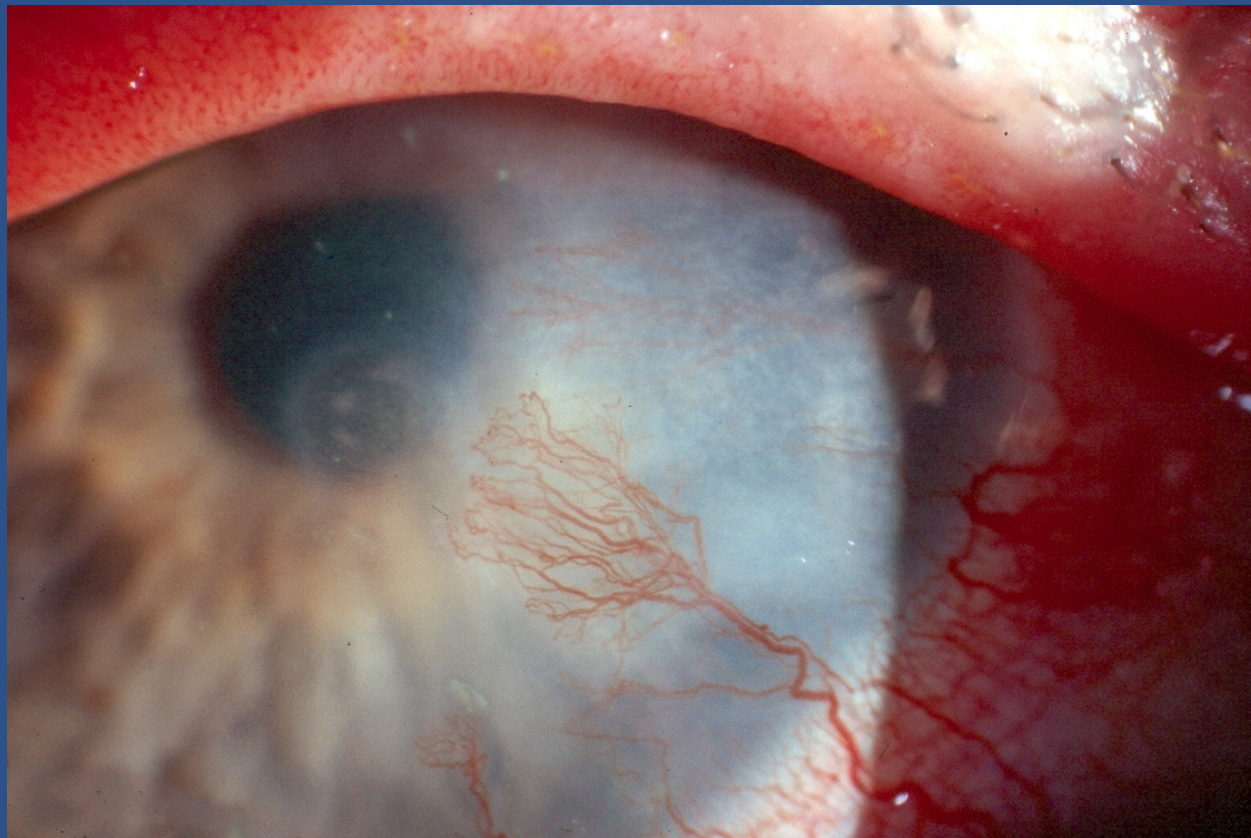
Added immunosuppression

- **Oral CsA?**
Long-term R_x may be effective
- **Oral Mycophenolate mofetil?**
Equal to CsA
- **Oral Tacrolimus?**
Relatively effective
- Lack of protocols combining 2 immunosuppressants!!!

Added immunosuppression

- **Topical CsA?**
At best = steroids.
- **Topical Tacrolimus?**
Potency > steroids?
- *Both may replace steroids in IOP-responders. Add-on benefit?*
No licensed product for ocular use.

New therapeutic target - neovessels



RCT. High-risk grafting I

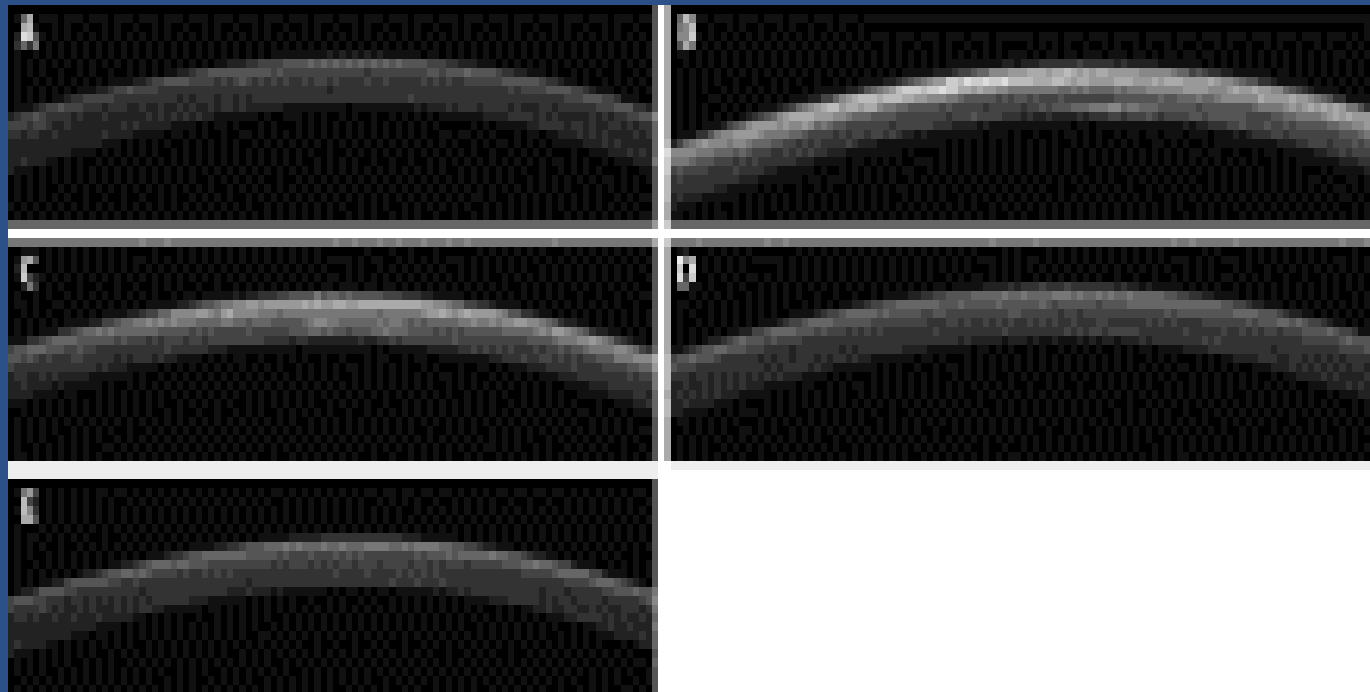
- Observer masking.
- Standard R_x with topical steroids.
- Add-on regimen studied.
- Active Comparator
- Avoid heterogenous populations!

RCT. High-risk grafting II

- Efficacy endpoints:
 - Rejection episodes within 2 - 3 yrs
 - Clear graft
 - Vascular activity
 - Visual Acuity
 - Pachymetry and ECD may be of value
 - VF questionnaire
- Safety variables:
 - Ocular (surface, IOP)
 - Systemic (hematology, liver, kidney)

"Corneal clarity"...

Scheimpflug imagery (JCRS 2010;36: 2105-2114)

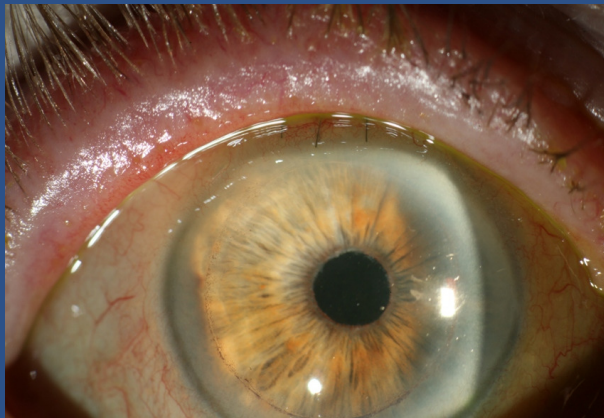


Slit lamp digital photos of neovessels

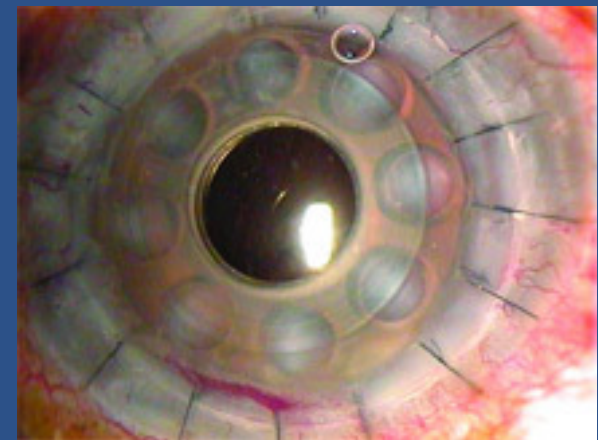


Other ways to avoid rejections

- Lamellar grafting



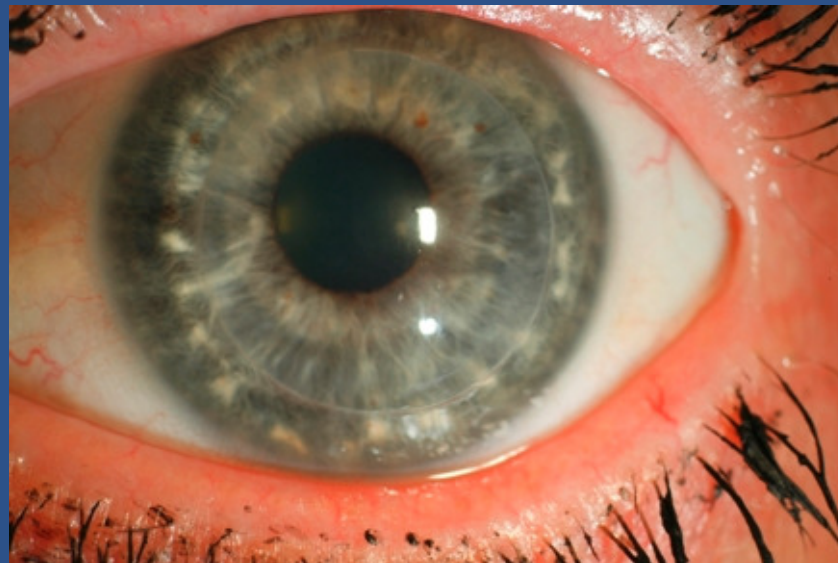
- Keratoprosthesis



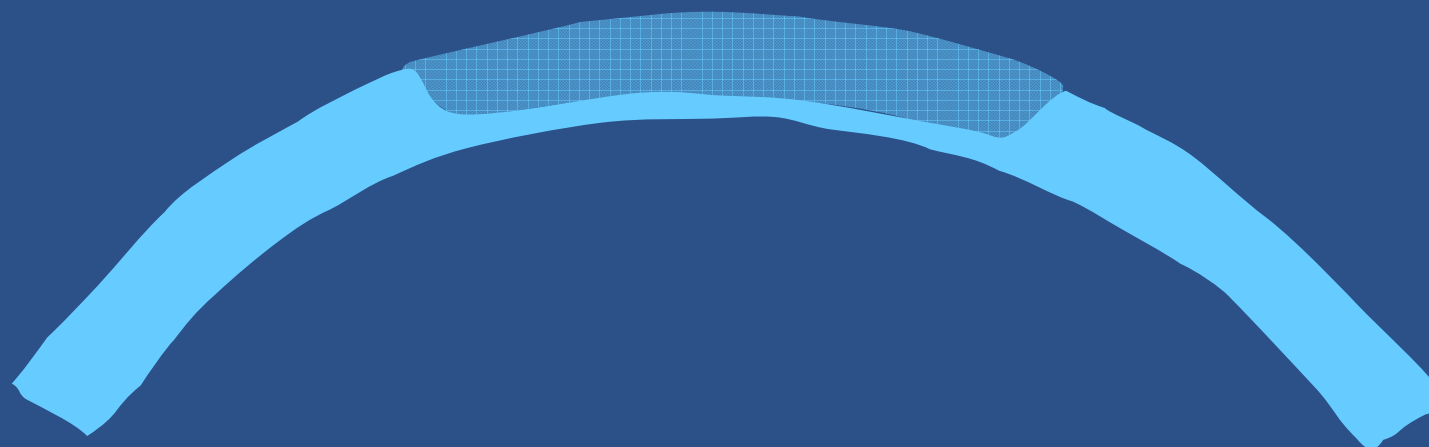
- Biosynthetic cornea

Anterior lamellar keratoplasty

- DALK replaces anterior cornea only
- No endothelial rejection!!!!!!
- Indications: Keratoconus, stromal dystrophies, non-penetrating scars

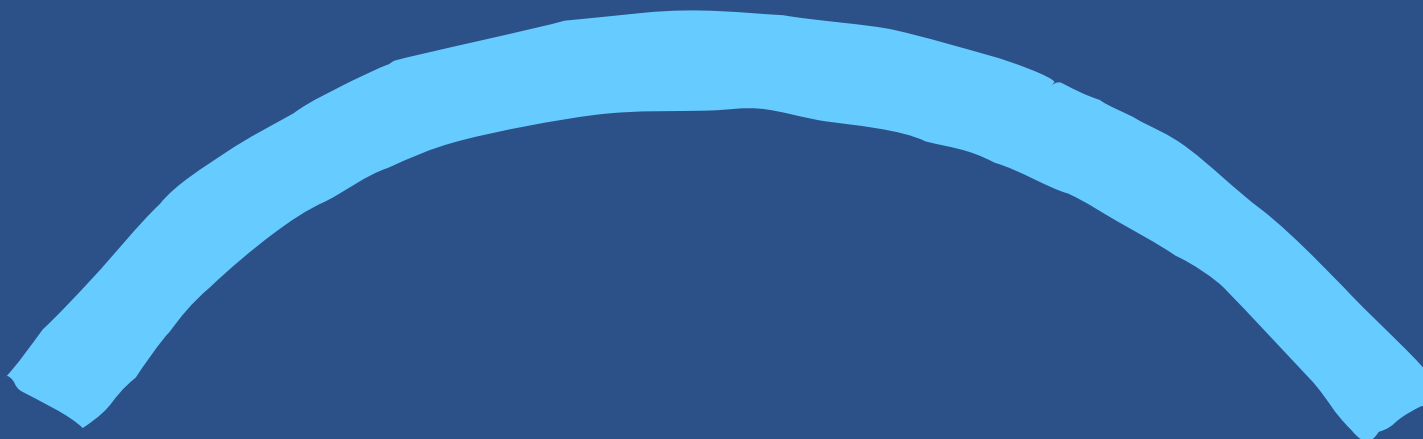


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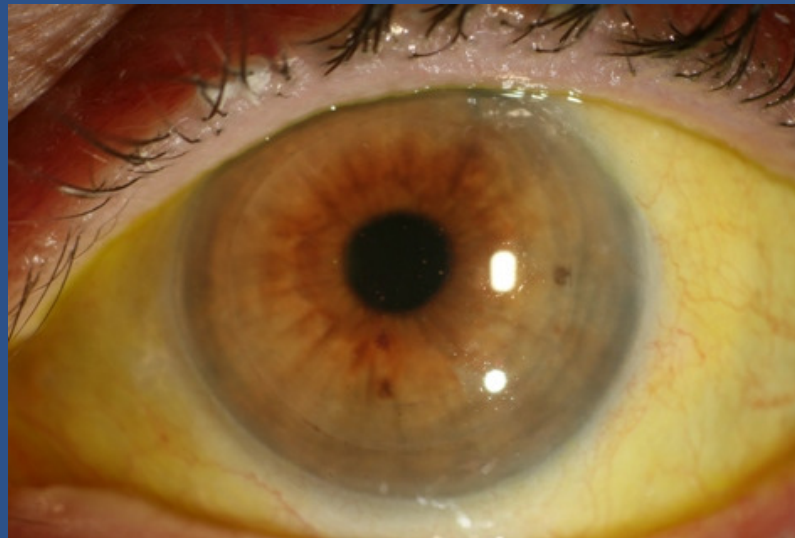
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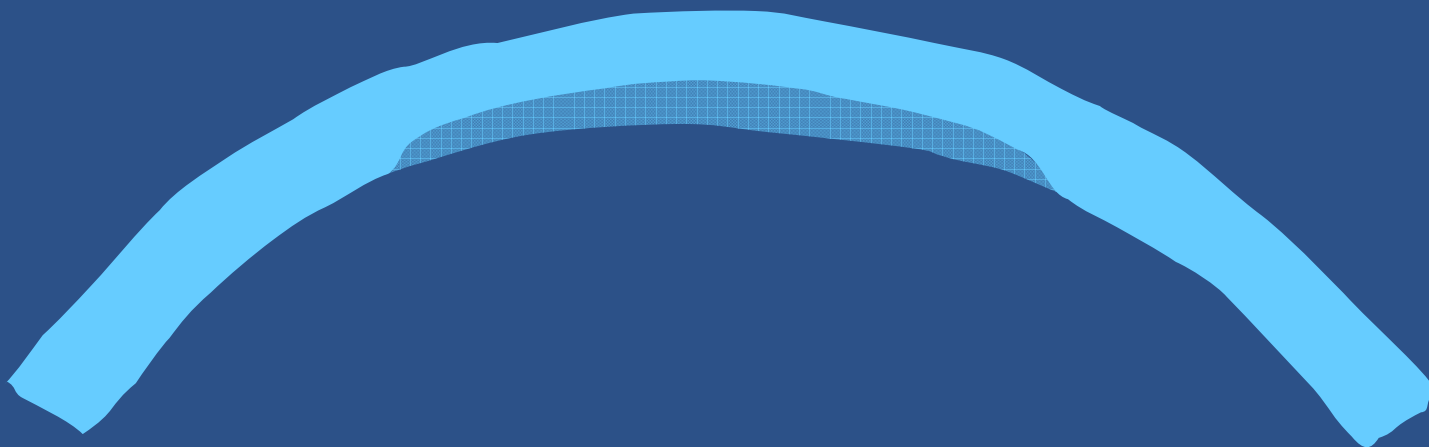


Posterior lamellar keratoplasty

- DSAEK, DMEK replaces endothelium
- Endothelial rejection.
Frequency < penetrating method?
Severity < penetrating method!

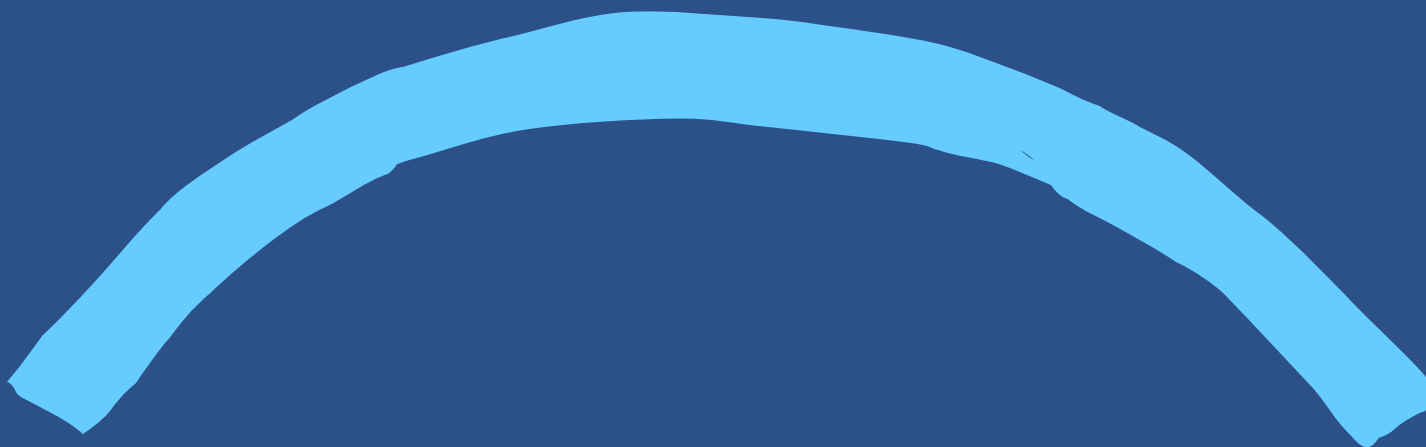


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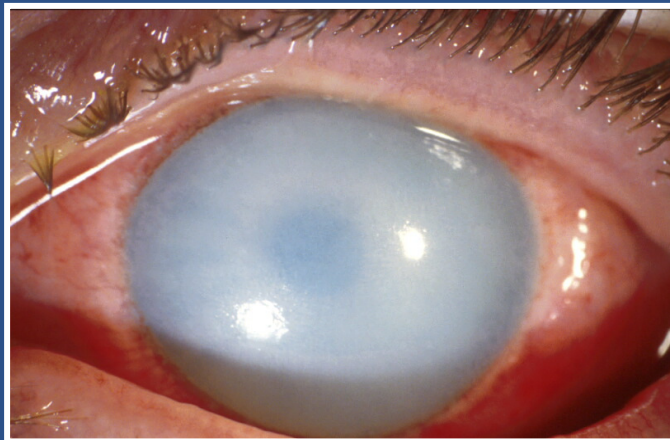
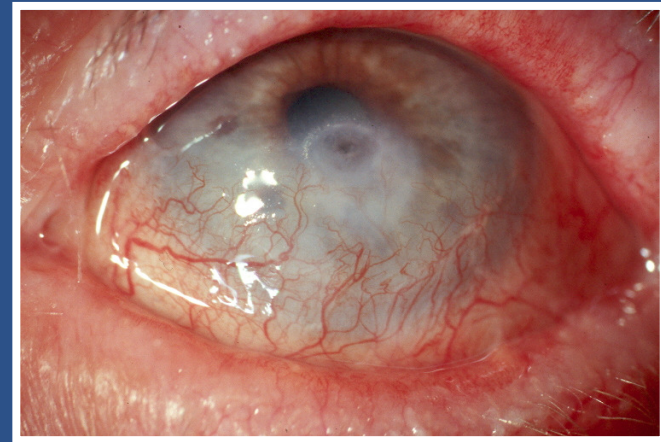
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Limbal stem cell deficiency (LSCD)

- Very rare conditions (Stevens-Johnson, OCP, aniridia)
- Ocular burn

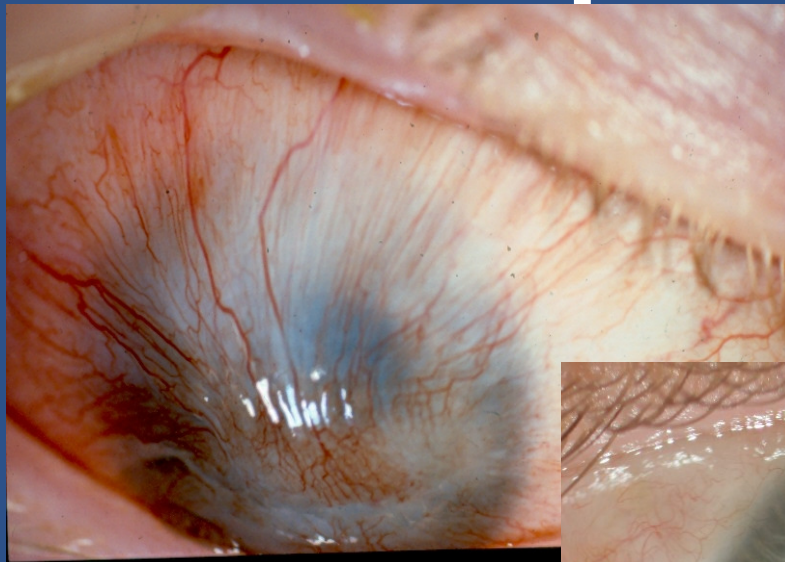


Dry eye – a contraindication to any restoration project

- Abort!



Unilateral disease. Autologous stem cell transplantation



Autologous explants



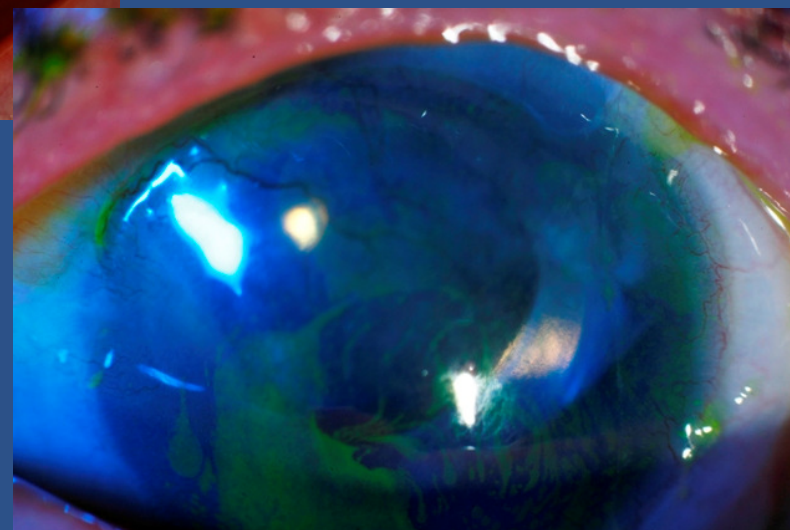
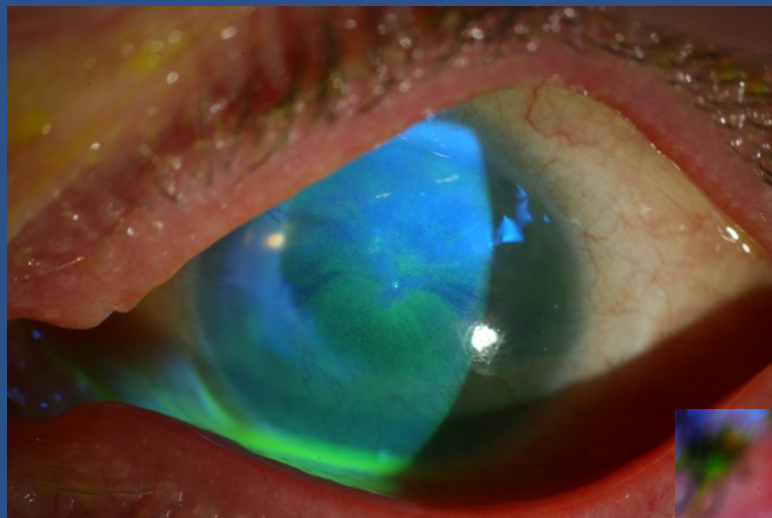
Post-op course with recurrence...



Allogeneic limbal stem cell transplantation



Post-op improvement



Ex vivo expansion of limbal stem cells

- Migration or separation of LSCs from a small limbal biopsy on a carrier.
- Animal products ususally involved
- Transfer to recipient eye easier AND limited use of autologous eye tissue.
- Cultivation in licensed cell laboratories!

Success of LCS grafting = a stable and avascular surface

- Autologous grafts: 75 – 100%
(free explants = cultivated cells)
- Allogeneic grafts: 30 – 75%
- Remaining poor vision may be restored
with keratoplasty

(R?)CT. Stem cell restoration a

- Observer masking.
Explant vs. culture?
Culture vs. culture?
Different immunosuppressive protocols
for allogeneic transplants?



(R?)CT. Stem cell restoration b

- Efficacy endpoints at 1 - 2 yrs:
Corneal epithelial parameters
(vital staining, superficial transparency,
regress of vessels).
Impression cytology?

VA
Pain, Photophobia
VF questionnaire
- Safety (*vide supra*)

Unmet needs. Summary

- Best topical steroid regime for low-risk grafts.
- Add-on value of topical immunosuppressants and/or anti-angiogenic R_x
- Systemic immunosuppression/ HLA-matching in high-risk grafting and allogeneic stem cell transplants.
- Development of gold standard cultivation of LSCs



