Ocular Surface Reconstruction: Where are we and where we should go

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Victor L. Perez, MD
Professor Ophthalmology
Director
Foster Center for Ocular Immunology at Duke Eye Center
Duke Medical University
Corneal Transplantation

Solid Organ Transplant

Corneal Transplant

![Graph of five-year survival rate of renal allografts against number of mismatched HLA alleles.]

![Graph showing probability of graft survival over trial time for different conditions: A: Keratoconus, B: Fuchs' Dystrophy, C: Other Dystrophies.]

![Image of an eye with corneal transplant.]

![Graph showing probability of graft survival over trial time for all grafts.]

The graphs illustrate the survival rates and probabilities for both renal and corneal transplants, highlighting the impact of HLA allele mismatches and different conditions affecting graft survival.
Corneal Transplantation: The Problem
Immune Mediated Corneal Endothelium Exhaustion Syndrome

Cytokines/Chemokines
Cellular Recruitment
(T Cells, mo)

Effector T Cells
Memory T Cells
Regulatory T Cells

T-Cell Priming

Ag/Ag+APC

Corneal Transplant

Innate Immune Responses
APC migration

Adaptive Immune Responses
Afferent Arm

Efferent Arm
Present Preventive Approach

Low Risk Transplants: Including Lamellar, DALK, DSEK and DMEK?

• Aggressive Topical Steroids after surgery 1 month
• Tapering and maintain chronic low dose Topical Steroid, considering use of “smart steroids” or Use of cyclosporine or tacrolimus
• Monitor IOP and Cataract Formation
Present Preventive Approach

• Intra-Operative IV Solumedrol (500mg-1000mg)

• Oral Prednisone 1mg/kg/day with tapering over a 1-2 months.

• T-Cell Inhibitor: Tacrolimus (.125mg/kg/day) for 1 year.

• Topical Steroids and Cyclosporine
Patients on Tacrolimus (n=10)

![Patients only on Tacrolimus](image)
Conclusions

Basic Models of In Vivo Visualization of Immune Responses in The Eye will open new mechanisms of inflammation/infection interactions in the cornea.

There are “Motility” Different Inflammatory Cell Populations in Corneal Grafts: Role of Host Microenvironment in Corneal Damage vs Protection?

Chronic Inflammatory Responses at the corneal transplant stromal level (T Cells and Macrophages) may be relevant and cause “Immune Mediated Corneal Endothelium Exhaustion Syndrome”

Anti-Chemokine Therapy and antimigration? Prevent Corneal Allograft Chronic Rejection.
LSCD: causes

• Chemical or thermal burn
• Multiple surgeries
• Radiation
• Anti-metabolites
• Contact lens wear
• Infections
• Neoplasia

• Steven Johnson syndrome
• Ocular cicatrizing pemphigoid
• Chronic limbitis
• Bullous keratopathy
• Neurotrophic keratopathy

• Aniridia
• Epidermal dysplasia
LSCD - Staging

- **Stage I**: normal epithelium in the central (5.0mm) cornea
  - A: < 50% of limbal involvement
  - B: ≥ 50% but <100% of limbal involvement
  - C: 100% of limbal involvement

- **Stage II**: central corneal epithelium involved
  - A: < 50% of limbal involvement
  - B: ≥ 50% but <100% of limbal involvement

- **Stage III**: 100% limbal and corneal involvement
Limbal Stem Cell Transplantation

- Restoration of Stem Cells in Ocular Surface Diseases
- Goal: Restore Phenotypic Corneal Epithelium to corneal surface, promote the barrier function of the limbus, improve corneal clarity.
Improving limbal graft survival

**Restoration of Ocular Surface Defense:**
**The First Strategy**

- **Aqueous Tear Deficiency**
  (Moderate to severe dryness)
  - Punctal occlusion, Autologous serum drops

- **Mechanical Irritation**
  (due to lid margin keratinization, entropion, meibomian gland orifice metaplasia, and misdirected lashes)
  - Plastic reconstruction, Topical retinoic acid, Scleral lens Mucous membrane graft

- **Exposure or Neurotrophic Keratopathy**
  - Botox-induced Ptosis, Tarsorrhaphy

- **Active Cicatricial Process**
  - Immunosuppression

## Surgical strategies

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratolimbal autograft</td>
<td>Contralateral limbus</td>
</tr>
<tr>
<td>Keratolimbal living related donor allograft</td>
<td>Living related donor limbus</td>
</tr>
<tr>
<td>Keratolimbal cadavaric allograft</td>
<td>Cadaveric corneoscleral rim</td>
</tr>
<tr>
<td>Ex vivo expansion autograft</td>
<td>Contralateral limbus</td>
</tr>
</tbody>
</table>

Limbal Stem Cell Deficiency

Unilateral

- Other Eye Normal
  - Keratolimbal Autograft

- Other Eye Abnormal
  - Go to Bilateral

Bilateral

- Less 50% LSCD
  - Keratolimbal
    - Living Related Allograft
    - MHC Matched + ImmuneSuppression

- More 50% LSCD
  - Keratolimbal
    - Cadaveric Allograft
    - ImmuneSuppression (combined)

Surv: 90-100%
No ImmuneSuppression
Surv: 0-52%
No ImmuneSuppression
Surv: 80-92%
Yes ImmuneSuppression
Surv: 0%
No ImmuneSuppression
Surv: 51-83%
Yes ImmuneSuppression
Limbal Stem Cell Therapy: Surgical Replacement
The Cincinnati Protocol for systemic immunosuppression after keratolimbal allograft
Poor cadaveric allograft survival

- 53 eyes (16 chemical burn, 9 SJS) - Mean follow up 34 months. If PK needed, cadaveric allograft then PK. Postop cyclosporine indefinitely.

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival Rate (± Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>76.9% ± 6.7%</td>
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<tr>
<td>2 years</td>
<td>66.5% ± 8.1%</td>
</tr>
<tr>
<td>3 years</td>
<td>47.4% ± 11.7%</td>
</tr>
<tr>
<td>5 years</td>
<td>23.7% ± 17.7%</td>
</tr>
</tbody>
</table>

Solomon et al. 2002.
# Efficacy of autograft

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cases</th>
<th>Median FU (months)</th>
<th>Improved VA (%)</th>
<th>Improved surface (%)</th>
<th>CLAU size</th>
<th>With AMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenyon and Tseng</td>
<td>21</td>
<td>23</td>
<td>81</td>
<td>95</td>
<td>240°</td>
<td>N</td>
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<tr>
<td>Rao et al</td>
<td>16</td>
<td>NA</td>
<td>69</td>
<td>94</td>
<td>60-90°</td>
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<tr>
<td>Moldovan et al</td>
<td>5</td>
<td>24</td>
<td>25</td>
<td>90</td>
<td>90-160°</td>
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<tr>
<td>Dua and Azaara-Blanco</td>
<td>6</td>
<td>19</td>
<td>100</td>
<td>100</td>
<td>120°</td>
<td>N</td>
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<tr>
<td>Meallet et al</td>
<td>5</td>
<td>22</td>
<td>100</td>
<td>100</td>
<td>240°</td>
<td>Y</td>
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<tr>
<td>Ivecovic et al</td>
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<td>16</td>
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<td>Santos et al</td>
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<td>33</td>
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<td>80</td>
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<td>Y</td>
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<tr>
<td>Kheirkhah et al</td>
<td>1</td>
<td>12</td>
<td>100</td>
<td>100</td>
<td>60°</td>
<td>Y</td>
</tr>
</tbody>
</table>

CLAU=conjunctival limbal autograft; FU= follow-up; LSCD=limbal stem cell deficiency; N=no; NA=not applicable; VA=visual acuity; Y=yes.

Liang et al. 2009.
What Limits the Use of Autologous Stem Cells

• Other Eye Affected
• Need to Many Limbal Stem Cells for Rehabilitation
• Clinical Evidence of a degree of limbal stem cell deficiency.
Limbal epithelial stem cell therapy

Sclerocorneal rims

Isolation and ex-vivo expansion of LESCs

Storage of LESCs
Request?
Seed cells into a transfer device
Surgery
Isolation and expansion procedure