Cornea on the Cutting Edge:
A Dazzling Dozen
Foundational and Future Innovations

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The Importance of Mentors

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Alan Carlson
Resurfacing the Back: Endothelial keratoplasty

Repairing the Surface: Amniotic membrane and simple limbal epithelial transplant

Reshaping for Refraction: Femtosecond laser (femto-Lasik, SMILE, femto arcuates)

Biomechanical Reinforcement: Intacs

Biomechanical Biochemical Strengthening: Surgical Crosslinking

“Cornea is the most noble of specialties”
1950s: Dr. Barraquer developed the first endothelial replacements

Not widely adopted due to technical challenges, KNV, and astigmatism.

1998: Dr. Gerrit Melles reported a posterior stromal pocket from a sclerolimbal approach with graft placement and an air bubble.

Dr. Mark Terry developed instrumentation and introduced it to the USA as deep lamellar endothelial keratoplasty (DLEK).

“In 10 years, we’re all going to be doing lamellar surgery almost exclusively”
DSEK

- 2004: Dr. Melles used descemetorhexis
- 2006: Dr. F.W. Price enhanced adherence with venting incisions.
- Dr. Gorovoy used a microkeratome to remove anterior stroma on the donor.
- Preparation of grafts by eye banks eliminates risks of mistakes.
- Thinner grafts (≤ 131 μm) improved visual outcomes. This led to the development of Ultrathin DSAEK (UT-DSAEK) and nanothin DSEK (40-60 micron grafts)


https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/DSAEEK/index.htm
2006: Melles used descemetorhhexis on donor corneas → stroma free graft that exactly replaces the removed tissue.

US eye banks now prepare DMEK grafts. Orientation is aided with Trypan blue dye and an “S or F”-stamp on the stromal side.
DMEK vs. DSAEK

- DMEK achieves slightly superior visual acuity and faster recovery.
- DMEK has more technical challenge (e.g., difficulty unscrolling and centering in the eye), surgical time, and intra- and postoperative complications.
  - Even experienced surgeons have rebubbling rates 5x higher than DSAEK.
- Steep learning curve for DMEK + excellent results and patient satisfaction achieved with DSAEK have slowed adoption of DMEK.

Amniotic membranes (AM) have anti-inflammatory, regenerative, non-immunogenic, and anti-scarring effects.

First use in eyes occurred in 1940s by Drs. DeRotth and Sorsby for chemical burns and symblepharon.

1992, Dr. Juan Batlle from Bascom Palmer revived its usage.

1997: Dr. Scheffer Tseng’s use of cryo-preservation for AM allowed long-term storage and ease of distribution.

Numerous applications: pterygium excision, conjunctival surface reconstruction, corneal ulcer (reepithelialization or temporary closure), and severe dry eye.

Limbal stem cells maintain corneal epithelial integrity and prevention of bulbar conjunctival invasion.

Depletion of limbal stem cells results in inflammation, pannus, and conjunctivalization leading to pain and decreased vision.

https://eyewiki.aao.org/Limbal_Stem_Cell_Deficiency


(Atallah et al., 2016)
Conjunctival limbal autografting (CLAU)
Keratolimbal allografts (KLAL)
Simple limbal epithelial transplantation (SLET)
Conjunctival limbal autografting (CLAU)

A. Diseased eye with LSCD

B. Pannus removed after peritomy

C. Healthy donor eye

D. Grafts collected from 12 and 6 o’clock positions

E. Grafts sutured in place

Keratolimbal allografts (KLAL):

- KLAL was utilizes cadaveric donor tissue for a 360-degree restoration with three limbal lenticules collected from 2 donor cadaveric eyes.

A Fibrovascular pannus removed from patient’s eye affected by LSCD
B Two allografts are collected from cadaveric donor eyes
C Three allograft lenticules are prepared
D Allograft lenticules are secured to the patient’s eye

Simple Limbal Epithelial Transplantation (SLET)

- Developed by Sangwan et al. in 2012 for unilateral LSCD treatment. Involves a 2 x 2 mm\(^2\) limbal tissue graft from the healthy fellow eye divided into 8-15 pieces and adhered to an amniotic membrane with fibrin glue.
- Less risk to donor site, low cost, and straightforward technique.
Simple Limbal Epithelial Transplantation (SLET)
Advantages in LASIK:

- More precise flap thickness and architecture
- Fewer flap complications
- Better uncorrected visual acuity
- Lesser likelihood of ocular aberrations

“Perfect”
• **SMall Incision Lenticule Extraction**
• Small incision 2-4 mm
• Flapless
• Good for patients with high myopia and severe dry eyes

• Up to -10.0D myopia
• Up to -5.0D myopic astigmatism
From Dan Reinstein, London Vision Clinic
- Precise corneal astigmatism correction
- Can be used for low astigmatism correction, in lieu of toric lenses, or to complement presbyopic toric lenses

KCN: Glasses & Contacts do not provide support

Intracorneal ring segments (ICRS) are PMMA implants made of synthetic material (PMMA).

Corneal channels for ICRS implantation may be performed manually or with femtosecond laser.
Table 17.1 Main characteristics of the intracorneal ring segments most commonly used in the clinical practice

<table>
<thead>
<tr>
<th>Design</th>
<th>Intacs</th>
<th>Kerarings</th>
<th>Ferrara</th>
<th>Intacs SK</th>
<th>Myoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arc length (degrees)</td>
<td>150°</td>
<td>90°–210°</td>
<td>90°–210°</td>
<td>150°</td>
<td>360°</td>
</tr>
<tr>
<td>Cross section</td>
<td>Hexagonal</td>
<td>Triangular</td>
<td>Triangular</td>
<td>Oval</td>
<td>Triangular</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>0.25–0.35</td>
<td>0.15–0.35</td>
<td>0.15–0.30</td>
<td>0.40–0.45</td>
<td>0.15–0.35</td>
</tr>
<tr>
<td>Inner diameter (mm)</td>
<td>6.77</td>
<td>6.00</td>
<td>4.8</td>
<td>6.00</td>
<td>5.00–8.00</td>
</tr>
<tr>
<td>Outer diameter (mm)</td>
<td>8.10</td>
<td>7.00</td>
<td>5.4</td>
<td>7.00</td>
<td>5.00–8.00</td>
</tr>
</tbody>
</table>
ICRS Outcomes

- Kmax:
  - 3 to 4 D flattening using 2 segments
  - 5 to 7 D astigmatism reduction using a single 450 segment
- Reduction in higher order aberrations (coma and coma-like).
- ICRS combined with corneal crosslinking is recommended for progressive keratoconus.


Corneal crosslinking: naturally occurs with time via Lysyl Oxidase, but is deficient in KCN.

Spoerl and Seiler at the U. Dresden used 370 nm ultraviolet A (UVA) light + Riboflavin (vitamin B<sub>2</sub>).
- Riboflavin: limits UVA penetration and act as a photosensitizer.

CXL:
- Stabilizes and halts progressive thinning
- improves stress-strain measurements
- increases stromal tissue enzymatic digestion resistance

Indications: keratoconus, PMD, terrien marginal degeneration, post-refractive ectasia, and non-healing corneal ulcers with corneal melting.
**Surgical Crosslinking (CXL)**

- **Dresden protocol:**
  - Epithelial debridement and a UVA dosage of 3mWcm² for 30 minutes (5.4 J/cm² in total) in eyes >400 μm (with epithelium off).
  - Risks: pain, corneal haze, scarring, reduced vision, infectious keratitis.

- **Epithelium on CXL (Epi-on CXL):**
  - Uses riboflavin formulations with enhanced permeability

- Accelerated, pulsed, oxygenation techniques to enhance efficacy are under investigation.
Meta-analysis of 12 RCTs and 966 total eyes was published in 2021 in Ophthalmology.

- **Epi-off:**
  - Superior reduction in Kmax (MD, 0.75; 95% CI, 0.23-1.28; \( P = 0.004 \))
  - Lower progression risk (2% vs. 7%) at 1 yr (RR, 4.49; 95% CI, 1.24-16.25, \( P = 0.022 \)).

- **Epi-on:**
  - Superior safety: 78% lower risk of significant, non-resolving complications (RR, 0.22; 95% CI, 0.06-0.79; \( P = 0.020 \)).

- No significant difference was found in UCDVA or CDVA

- Epi-on can be combined with simultaneous Intacs
**SIMULTANEOUS INTACS AND EPI-ON RESULTS**

- **Patient 1**
  - Preoperative
    - Kmax: 57.37 D
    - Astig: 5.25 D
  - 1 mo Postoperative
    - Kmax: 55.19 D
    - Astig: 2.89 D

- **Patient 2**
  - Preoperative
    - Kmax: 59.52
    - Astig: 8.24 D
  - 1 mo Postoperative
    - Kmax: 54.53 D
    - Astig: 4.44 D

- **Patient 3**
  - Preoperative
    - Kmax: 47.13 D
    - Astig: 2.49 D
  - Postoperative
    - Kmax: 44.12 D
    - Astig: 1.67 D
Top 7 Upcoming Innovations

- Pharmacologic crosslinking (iVeena)
- Nerve regeneration
- Endothelial cell replacement (Shigeru Kinoshita)
- Gene therapy
- Acufocus IC8
- Femtosecond IOL Modification (Clerio, PerfectLens)
- Allogenic implants (Allotex; LIKE by F. Price)

“Change is the only constant”
LOX is a copper dependent enzyme that catalyzes collagen crosslinks.

LOX activity is diminished in Keratoconic corneas (Pahuja et al, IOVS 2016) (Shetty et al, JRS 2019).

Copper Enhances LOX Activity in Human Corneal Fibroblasts.
President & co-Founder of iVeena
**Aim**
- Treatment of keratoconus with an eyedrop not requiring surgery or light

**Target Patients**
- 31 Patients with keratoconus or post-LASIK ectasia

**Efficacy**
- Mean and maximal corneal keratometry
- Best corrected visual acuity

**Safety**
- Adverse Events

**Dosing**
- Twice a day drops, with 3 subarms for vehicle, 6 weeks of IVMED-80, or 16 weeks of IVMED-80

**Key Inclusion Criteria**
- Maximum corneal keratometry of 45 D to 68 D
- Minimum corneal thickness > 350 microns

**Key Exclusion Criteria**
- Significant central corneal scarring or hydrops
- Presence of pre-existing glaucoma, uveitis, uncontrolled diabetic retinopathy, or prior ocular trauma or prior intraocular surgery
- Previous cornea surgeries
IVMED-80 reduces Kmax

- Baseline adjusted Kmax at 26 weeks
  - Placebo: increase of 0.22 D
  - IVMED-80 for 6 weeks: No significant effect
  - IVMED-80 for 16 weeks:
    - decrease of 1 D at 16 weeks, 0.78 D at 26 weeks (p = 0.01991)
SSI (p=0.029) and SP-HC (p=0.018) improved on Oculus Corvis analysis.
No treatment-related Adverse Events.

One unrelated Adverse Event - placebo group (mild marginal keratitis).
First eyedrop for keratoconus.
Zero treatment related adverse events.
Clinically relevant Corneal flattening sufficient to meet FDA benchmark.
Longer treatment yields more flattening and treatment effect seems to persist after cessation.
Neurotrophic keratopathy – decreased or absent corneal sensation due to damage of trigeminal nerve
- epithelial breakdown, ulceration, perforation

Topical Chemokines
- Thymosin β4
- Oxervate (Cenegermin; NGF analogue)

Surgical
- Neurotization
• 43-amino acid naturally occurring molecule
• Anti-inflammatory effects by suppressing NF-κB and TNF-α
• Promotes re-epithelialization within 4 weeks

(Dunn et al. Arch Ophthalmol 2010)

Gabriel Sosne

Hynda Kleinman
ONLY FDA-approved drug for treatment of neurotrophic keratitis (approved in 2018)

MOA: Recombinant human nerve growth factor


Rita Levi-Montalcini
Two clinical trials
- NGF0212 (REPARO) in Europe

Pflugfelder SC et al. Ophthalmology. 2020

Bonini S et al. Ophthalmology. 2018
- Surgical translocation of donor nerve to the perilimbal cornea
- This is a slow process, with nerves growing at 1 mm/day
- Healing usually takes a few months
- Check sensation of nerves (supraorbital, supratrochlear, infraorbital, greater auricular nerves)
- Length and distance of donor nerves (should be tension-free to allow growth)
Contralateral supraorbital and supratrochlear branches were used.

Allograft vs Autografts (both are effective at grafting) (Sweeney et al. Br. J Ophthalmol 2020)

Connecting nerves
  - Sensory sural, greater auricular, lateral antebrachial cutaneous, contralateral supratrochlear, supra/infraorbital nerves

Liu CY et al. Ocul Surf. 2021
>80% corneal sensation restoration and resolution of numbness within 6 to 8 months

- Perform procedure early to minimize scarring
- Corneal transplantation is usually done 2 years after neurotization (if needed)
Endothelium: monolayer with 2000-3500 cells/mm$^2$

Cellular pumps create a net flux of ions from stroma to aqueous to dehydrate the stroma and ensure corneal clarity.
Corneal Endothelial Therapies

“Spare your motions”

Restorative

Cell-based

Gene therapies
Promotes engraftment of endothelial cells

Cultured primary cells from donors + ROCK inhibitors were injected into anterior chamber. At 24 weeks post op:

- increased endothelial cell density,
- decreased thickness (<640 micron)
LONG-TERM EFFECTS OF ENDOTHELIAL CELL REPLACEMENT

(Numa et al. Ophthalmol 2021)
ZEB1 mutation in posterior polymorphous corneal dystrophy
SLC4A11 mutation in congenital hereditary endothelial dystrophy
KRT12 mutation in Meesmann corneal dystrophy
TGFBI mutation in granular corneal dystrophy
COL8A2 mutation in Fuchs endothelial corneal dystrophy
• Tiny round cysts forming in the epithelium
• Reduce expression of mutant KRT12 mRNA and protein using CRISPR-Cas9; *In vivo* testing was performed by injection into stroma of mice
• Demonstrated the first in vivo gene editing in cornea CRISPR-Cas9 (Courtney DG et al. *Gene Ther* 2016)
Multiple granular deposits in corneal stroma caused by genetic and noninflammatory disease of the cornea

CRISPR-Cas9 mediated gene therapy was shown in primary keratocytes taken from patients with GCD

Collagen type VIII alpha 2 chain (COL8A2) missense mutation affects corneal endothelium → onset of Fuchs

Target the mutated COL8A2 Start Codon with CRISPR-Cas9 to reduce mutated protein expression → reduces endothelial death and rescues endothelial function

Start codon disruption with CRISPR/Cas9 prevents murine Fuchs’ endothelial corneal dystrophy

Hironori Uehara¹, Xiaohui Zhang¹, Felipe Pereira², Siddharth Narendran², Susie Choi¹, Sai Bhuvanagiri³, Jinlu Liu³, Sangeetha Ravi Kumar¹, Austin Bohner³, Lara Carroll³, Bonnie Archer¹, Yue Zhang⁴, Wei Liu⁵, Guangping Gao⁶, Jayakrishna Ambati², Albert S Jun⁷, Balamurali K Ambati¹
Uehara et al. eLife 2021

Fuchs Dystrophy AAV Gene Therapy

Reduces endothelial cell decline
Reduces guttate formation
• Extended range of vision (distance, intermediate, near without blurry zone)
• Accommodate up to 1.50D pre-existing astigmatism

• Good for post-RK patients and other corneal scarring patients

https://theophthalmologist.com/subspecialties/the-ic-8-iol-big-advantages-through-small-apertures
X: AcuFocus IC-8 IOL
PerfectLens
- Based on Refractive Index Shaping (RIS).
- Laser cause acrylic material to become hydrophilic changing the refractive characteristics.
- This can create a “lens” within a 50μm area inside an IOL.
- Achieves +/-0.1 D resolution, up to 7.60 D of toric change, and changes multifocal into a monofocal or vice versa.

http://www.perfectlens.com/index.htm
LIRIC (Clerio)

- Laser-Induced Refractive Index Change
- Femtosecond laser at a low energy causes localized material density and refractive index changes.
- Advantages vs LASIK: thinner cornea candidates and less corneal nerve damage.
- Human trials have been conducted with positive preliminary results.
  - Up to 9.5 D of refractive index change
  - 0.05 D resolution
  - Monofocal to multifocal and vice versa


Vukich J. The LIRIC Platform: Laser Induced Refractive Index Change for Refractive Error Correction.
TransForm Corneal Allograft (Allotex)
- Sterilized, acellular corneal lenticules
- Made with eye bank tissues shaped by excimer.
- Reversible and minimally invasive.
- Placed under a standard LASIK flap.
- In a multi-center clinical trial for presbyopia correction in Europe.

https://allotex.com/
LIKE for hyperopia (F. Price)

- Lenticular Intrastromal Keratoplasty
- Enables correction of 3-8 D of Hyperopia.
- Can be combined with CXL for KCN
- Prepared lenticules may be ordered from Gebauer
- Place under LASIK flap and wait 2 mos.
- The flap is relifted for excimer ablation.

https://www.gebauermedical.com/procedures/like-for-hyperopia
Thank you to ORBIS
THANK YOU

- Andrew Thomson
- Quyen Luong
- Bonnie Archer
- Sarah Molokhia