XV
Corso Nazionale

SIBO
Società Italiana Banche degli Occhi

RESPONSABILI SCIENTIFICI:
Massimiliano Corneli
Silvia Conforti

13 Maggio
2023

FABRIANO

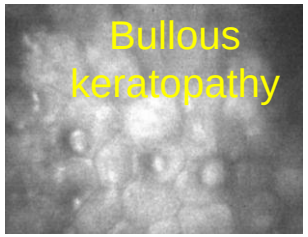
Eye Banking : evoluzione futura tra scienza e fantascienza

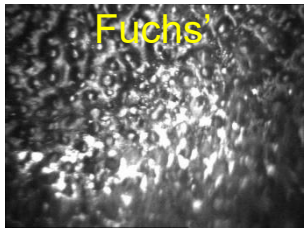
Stefano Ferrari & Diego Ponzin

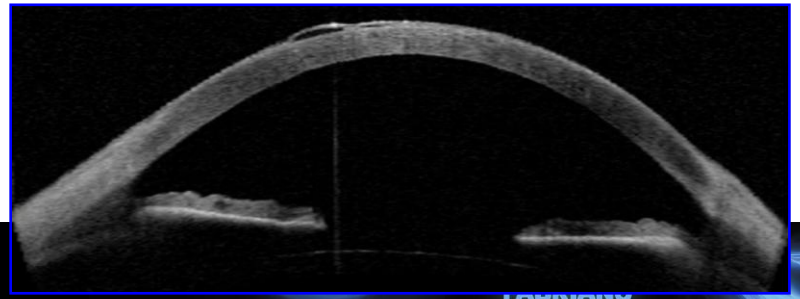
Fondazione Banca degli Occhi del Veneto, Venezia

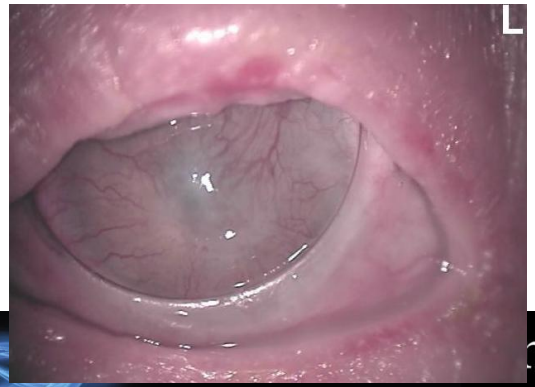
Eye banking and corneal / ocular surface diseases

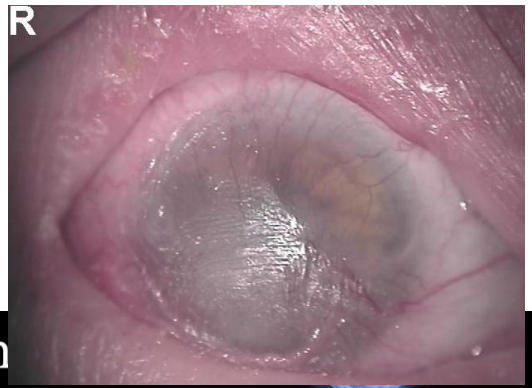
- Permanent structures:
  - ✓ Stroma
  - ✓ Endothelium
- Regenerating / healing structures:
  - ✓ Corneal epithelium / limbus
  - ✓ Conjunctival epithelium





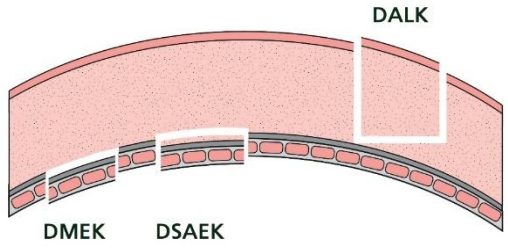


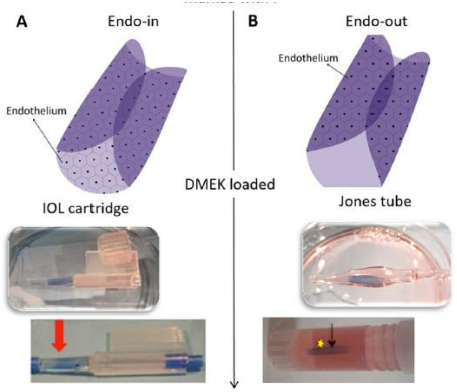




Keratoplasty: current paradigma

- Replacing only the diseased layers:
  - ✓ Severe corneal involvement: PK (curvature sensitive)
  - ✓ Stromal disease: deep anterior LK (↓ immune rejection, ↓ graft failure)
  - ✓ Endothelial dysfunction: EK (maintains corneal integrity and curvature, ↓ endothelial rejection)
- Iatrogenic graft failure distinct from primary graft failure
- **DSAEK**: ~refractive-neutral procedure, **most common EK**
- Safe surgery, fast visual recovery, good **VA**





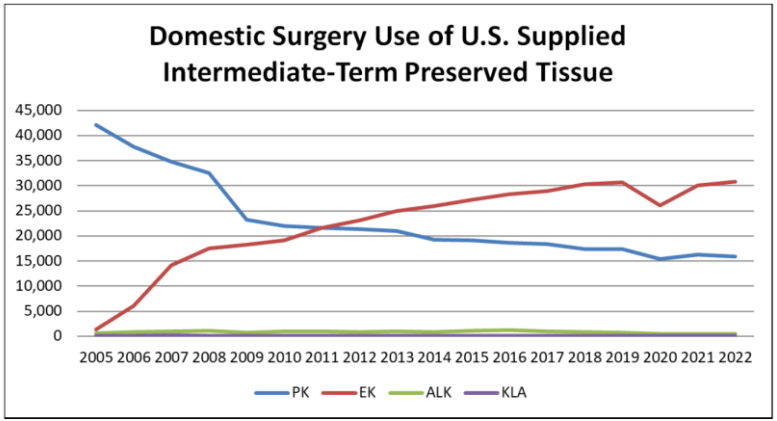
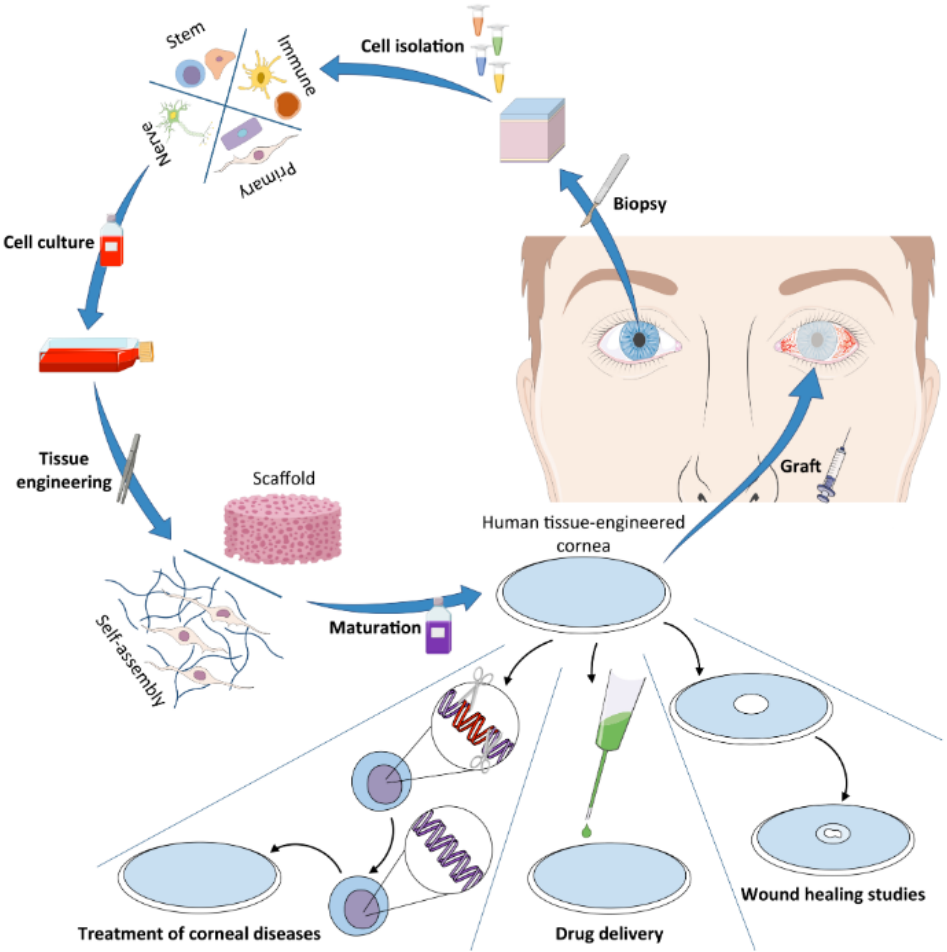


Figure 3: Domestic PK vs. EK vs. ALK Surgery Trends 2005-2022.

Tan DT, et al. Corneal transplantation. *Lancet* 2012;379:1749-61.

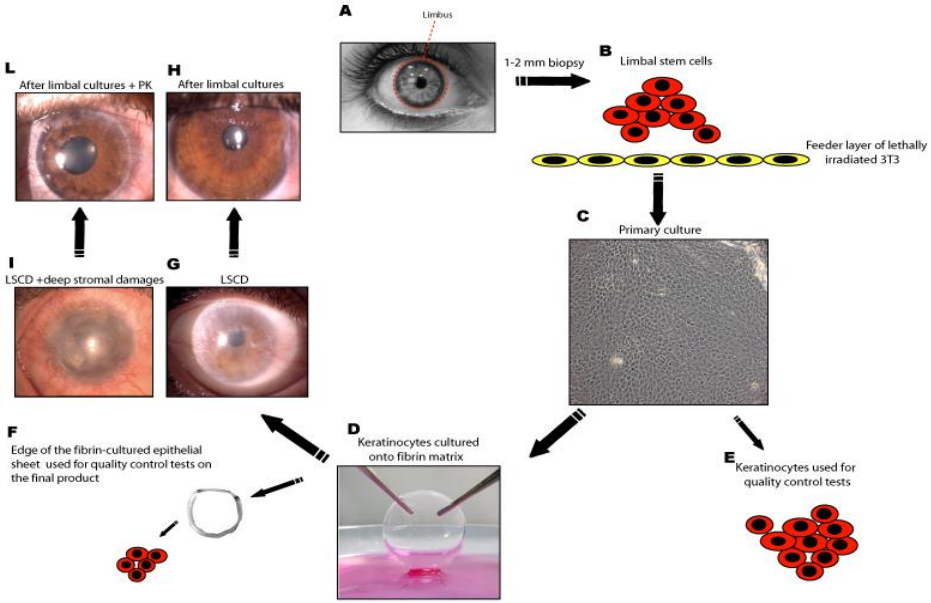
The Eye Bank Association of America. EBAA 2022 statistical report, 2023.

WILL HUMAN TISSUE-ENGINEEERED CORNEAS BE THE WAY FORWARD IN THE FUTURE?

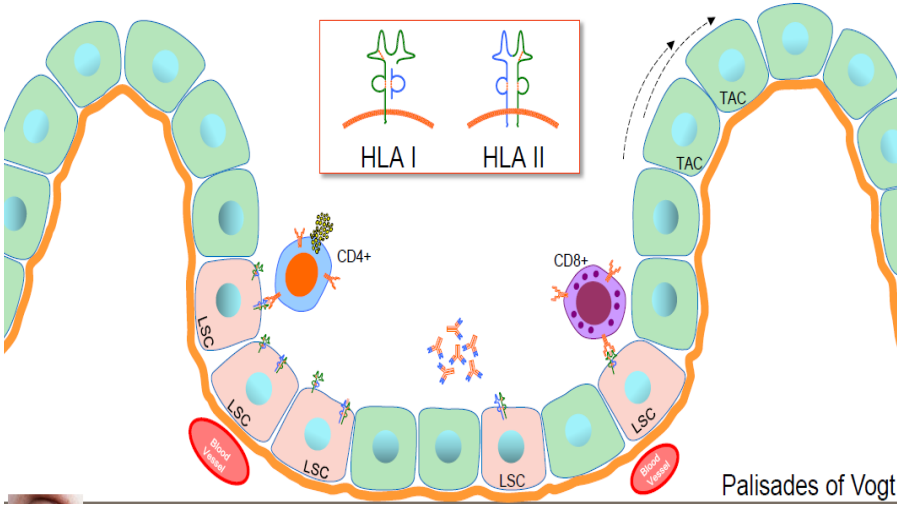


APPROACHES FOR CORNEAL EPITHELIUM REGENERATION (I): LSC transplantation

autologous cell therapy



allogeneic cell therapy



Genetic Modification of Limbal Stem Cells to Decrease Allogeneic Immune Responses

Emilio Valdivia[1], Marina Bertolin[2], Claudia Breda[2], Marco Carvalho Oliveira[1], Anna Katharina Salz[3], Nicola Hofmann[3], Martin Börgel[3], Rainer Blasczyk[1], Stefano Ferrari[2] and Constanca Figueiredo[1]*

APPROACHES FOR CORNEAL EPITHELIUM REGENERATION (II): newer eye drops

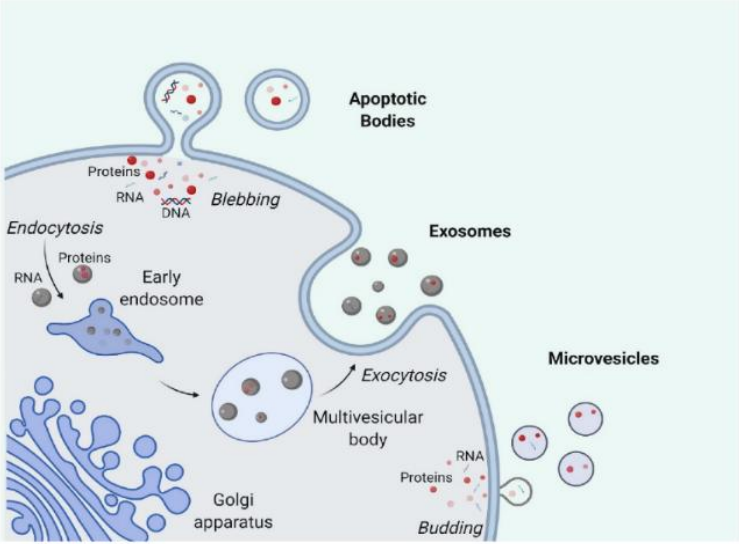
cells

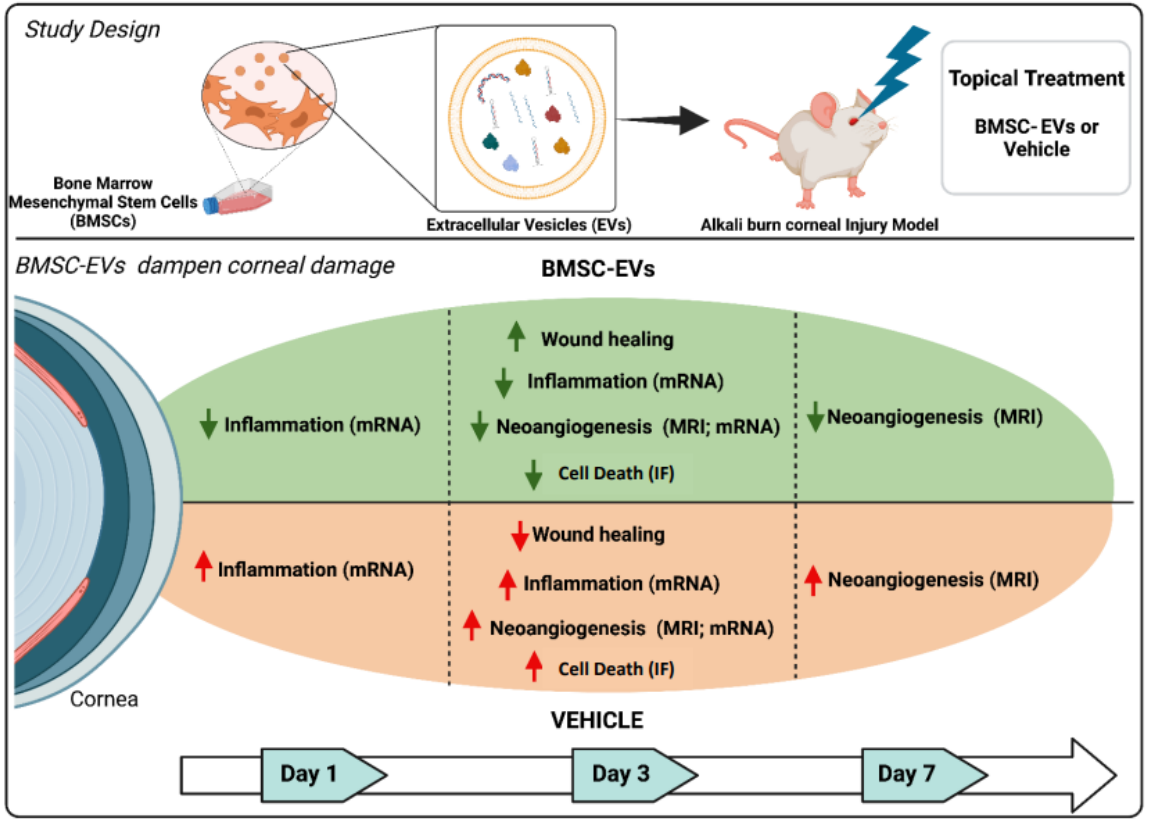
MDPI

Article

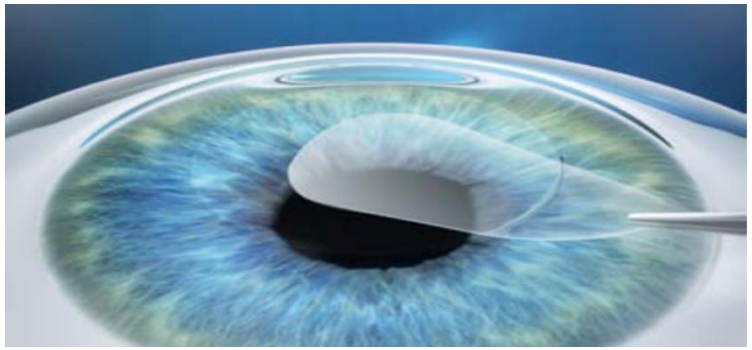
Bone Marrow Mesenchymal Stromal/Stem Cell-Derived Extracellular Vesicles Promote Corneal Wound Repair by Regulating Inflammation and Angiogenesis

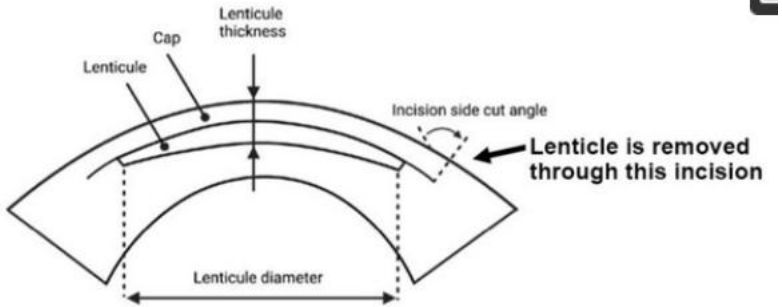
Gabriele Saccu [1,†], Valeria Menchise [2,†], Chiara Gai [3], Marina Bertolin [4], Stefano Ferrari [4], Cristina Giordano [5], Marta Manco [1], Walter Dastrù [1], Emanuela Tolosano [1], Benedetta Bussolati [1], Enzo Calautti [1], Giovanni Camussi [3], Fiorella Altruda [1,*] and Sharmila Fagoonee [2,*]

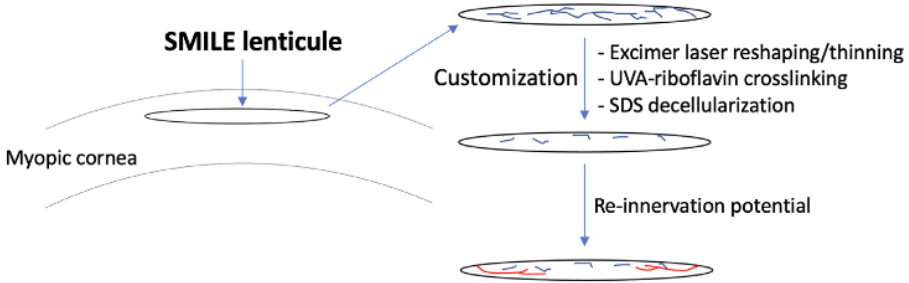




APPROACHES TO MODIFY THE STROMA (I) – banking of SMILE lenticules







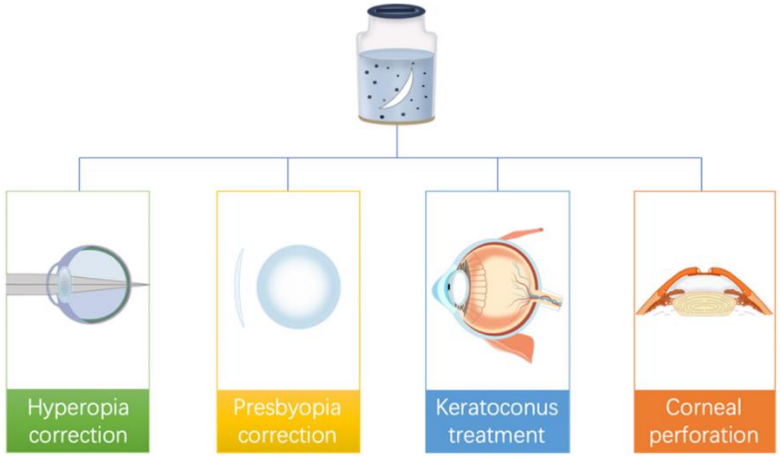


Fig. 2. Illustrations of the clinical applications of SMILE-derived lenticule.

APPROACHES TO MODIFY THE STROMA (II) – synthetic scaffolds

ARTICLES
https://doi.org/10.1038/s41587-022-01408-w
nature biotechnology

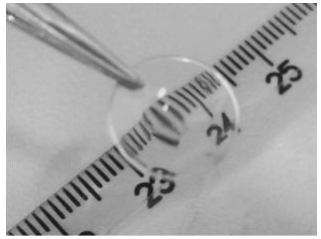
Check for updates

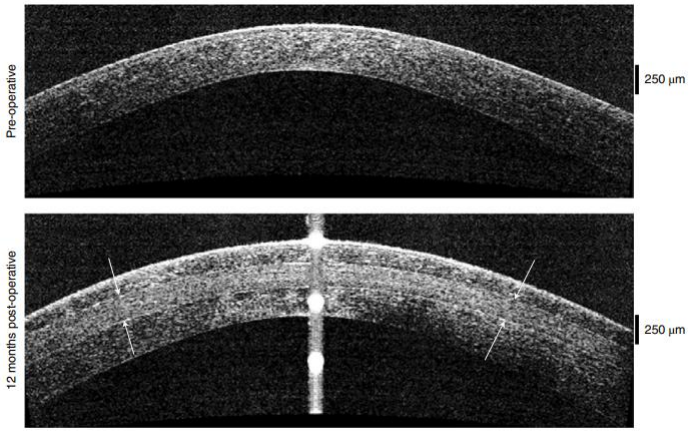
OPEN

Bioengineered corneal tissue for minimally invasive vision restoration in advanced keratoconus in two clinical cohorts

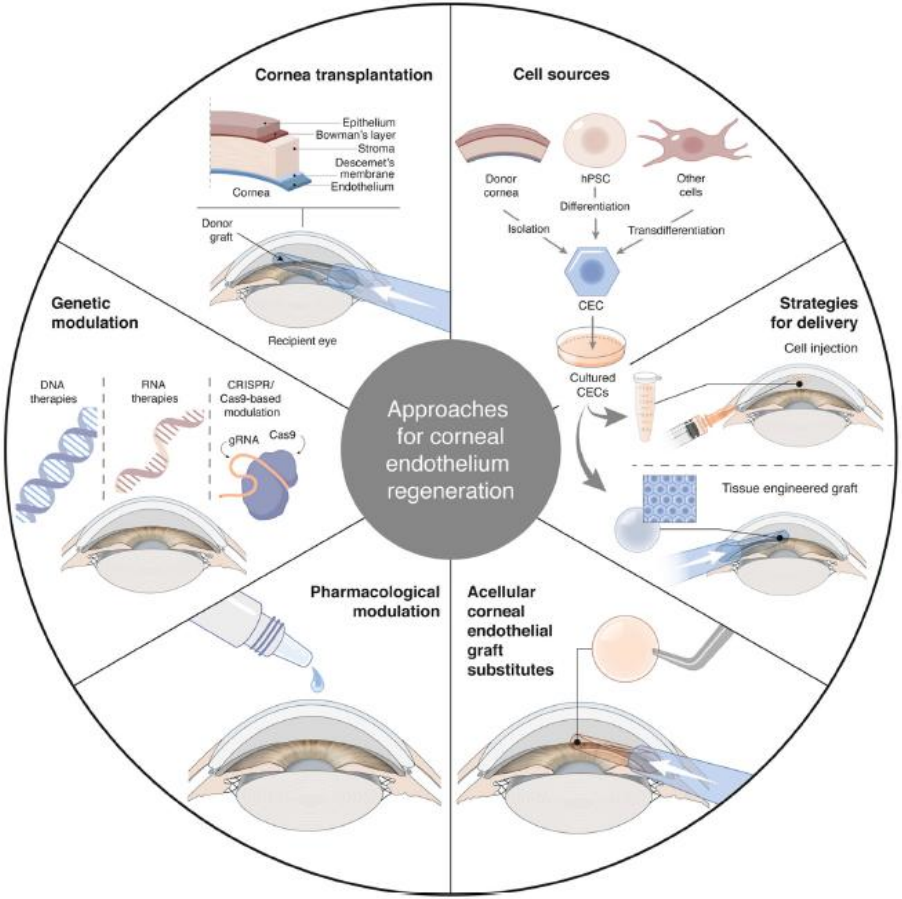
Mehrdad Rafat[1,2,7] ✉, Mahmoud Jabbarvand[3,7], Namrata Sharma[4,7], Maria Xeroudaki[5], Shideh Tabe[1], Raha Omrani[1], Muthukumar Thangavelu[1], Anthony Mukwaya[5], Per Fagerholm[5], Anton Lennikov[5], Farshad Askarizadeh[6] and Neil Lagali[5,7] ✉

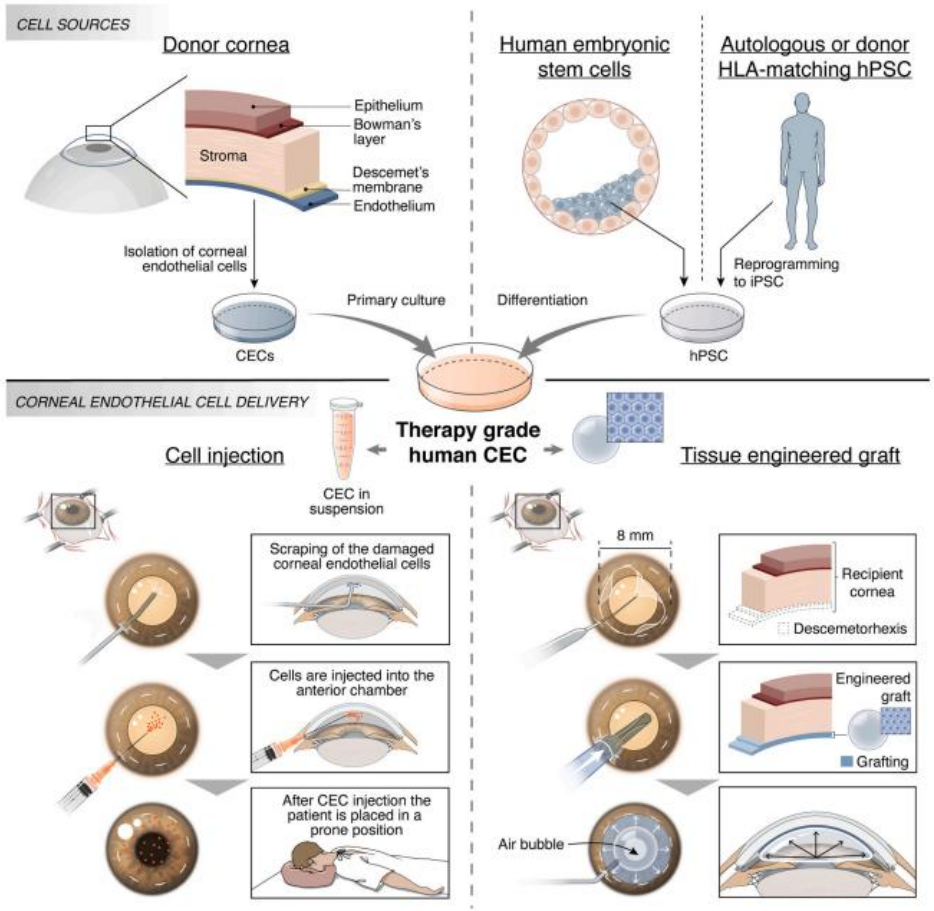
Visual impairment from corneal stromal disease affects millions worldwide. We describe a cell-free engineered corneal tissue, bioengineered porcine construct, double crosslinked (BPCDX) and a minimally invasive surgical method for its implantation. In a pilot feasibility study in India and Iran (clinicaltrials.gov no. NCT04653922), we implanted BPCDX in 20 advanced keratoconus subjects to reshape the native corneal stroma without removing existing tissue or using sutures. During 24 months of follow-up, no adverse event was observed. We document improvements in corneal thickness (mean increase of 209 ± 18 µm in India, 285 ± 99 µm in Iran), maximum keratometry (mean decrease of 13.9 ± 7.9 D in India and 11.2 ± 8.9 D in Iran) and visual acuity (to a mean contact-lens-corrected acuity of 20/26 in India and spectacle-corrected acuity of 20/58 in Iran). Fourteen of 14 initially blind subjects had a final mean best-corrected vision (spectacle or contact lens) of 20/36 and restored tolerance to contact lens wear. This work demonstrates restoration of vision using an approach that is potentially equally effective, safer, simpler and more broadly available than donor cornea transplantation.





OCT scans indicating sustained thickening and regularization of corneal curvature following implantation of 280-µm-thick BPCDX (anterior and posterior surfaces of BPCDX indicated by white arrows).


Cornea transplantation
Epithelium
Bowman's layer
Stroma
Descemet's membrane
Endothelium
Cornea
Donor graft
Recipient eye
Cell sources
Donor cornea
hPSC
Other cells
Differentiation
Isolation
Transdifferentiation
CEC
Cultured CECs
Strategies for delivery
Cell injection
Tissue engineered graft
Genetic modulation
DNA therapies
RNA therapies
CRISPR/ Cas9-based modulation
gRNA
Cas9
Approaches for corneal endothelium regeneration
Pharmacological modulation
Acellular corneal endothelial graft substitutes


CELL SOURCES
Donor cornea
Epithelium
Bowman's layer
Stroma
Descemet's membrane
Endothelium
Isolation of corneal endothelial cells
CECs
Primary culture
Human embryonic stem cells
Autologous or donor HLA-matching hPSC
Reprogramming to iPSC
Differentiation
hPSC
CORNEAL ENDOTHELIAL CELL DELIVERY
Cell injection
CEC in suspension
Therapy grade human CEC
Tissue engineered graft
Scraping of the damaged corneal endothelial cells
Cells are injected into the anterior chamber
After CEC injection the patient is placed in a prone position
8 mm
Recipient cornea
Descemetorhexis
Engineered graft
Grafting
Air bubble

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PLOS ONE

A Cost-Minimization Analysis of Tissue-Engineered Constructs for Corneal Endothelial Transplantation

Tien-En Tan[1,2]*, Gary S. L. Peh[3], Benjamin L. George[3], Howard Y. Cajucom-Uy[4], Di Dong[5], Eric A. Finkelstein[5,6], Jodhbir S. Mehta[2,3,7]

1 Yong Loo Lin School of Medicine, National University of Singapore, Singapore, **2** Singapore National Eye Centre, Singapore, **3** Tissue Engineering and Stem Cell Group, Singapore Eye Research Institute, Singapore, **4** Singapore Eye Bank, Singapore, **5** Health Services and Systems Research, Duke-NUS Graduate Medical School, Singapore, **6** Lien Centre for Palliative Care, Singapore, **7** Department of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore

Abstract

Corneal endothelial transplantation or endothelial keratoplasty has become the preferred choice of transplantation for patients with corneal blindness due to endothelial dysfunction. Currently, there is a worldwide shortage of transplantable tissue, and demand is expected to increase further with aging populations. Tissue-engineered alternatives are being developed, and are likely to be available soon. However, the cost of these constructs may impair their widespread use. A cost-minimization analysis comparing tissue-engineered constructs to donor tissue procured from eye banks for endothelial keratoplasty was performed. Both initial investment costs and recurring costs were considered in the analysis to arrive at a final tissue cost per transplant. The clinical outcomes of endothelial keratoplasty with tissue-engineered constructs and with donor tissue procured from eye banks were assumed to be equivalent. One-way and probabilistic sensitivity analyses were performed to simulate various possible scenarios, and to determine the robustness of the results. A tissue engineering strategy was cheaper in both investment cost and recurring cost. Tissue-engineered constructs for endothelial keratoplasty could be produced at a cost of US$880 per transplant. In contrast, utilizing donor tissue procured from eye banks for endothelial keratoplasty required US$3,710 per transplant. Sensitivity analyses performed further support the results of this cost-minimization analysis across a wide range of possible scenarios. The use of tissue-engineered constructs for endothelial keratoplasty could potentially increase the supply of transplantable tissue and bring the costs of corneal endothelial transplantation down, making this intervention accessible to a larger group of patients. Tissue-engineering strategies for corneal epithelial constructs or other tissue types, such as pancreatic islet cells, should also be subject to similar pharmacoeconomic analyses.

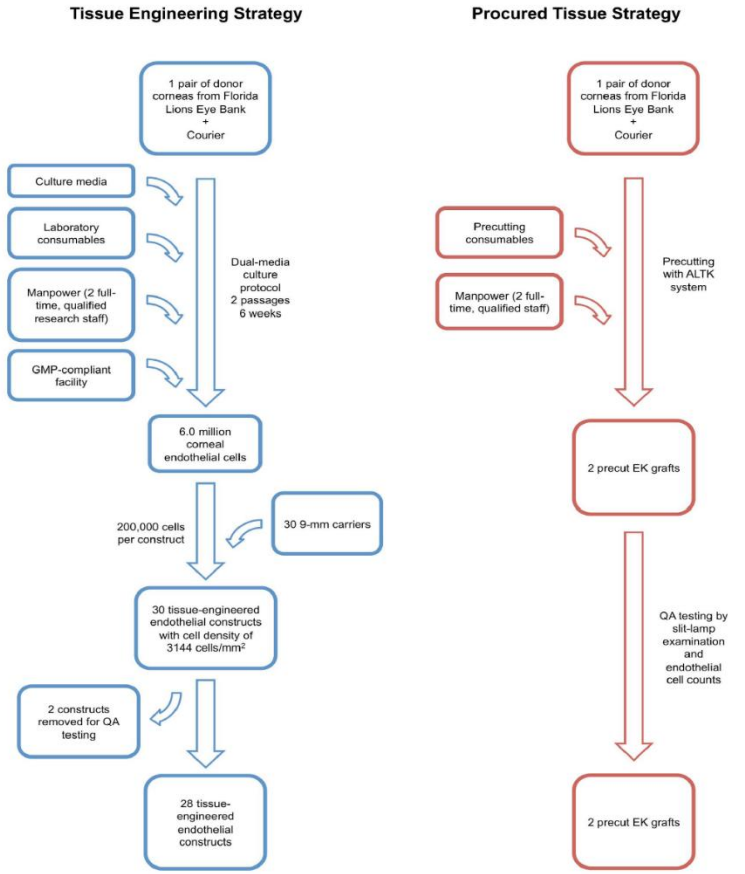
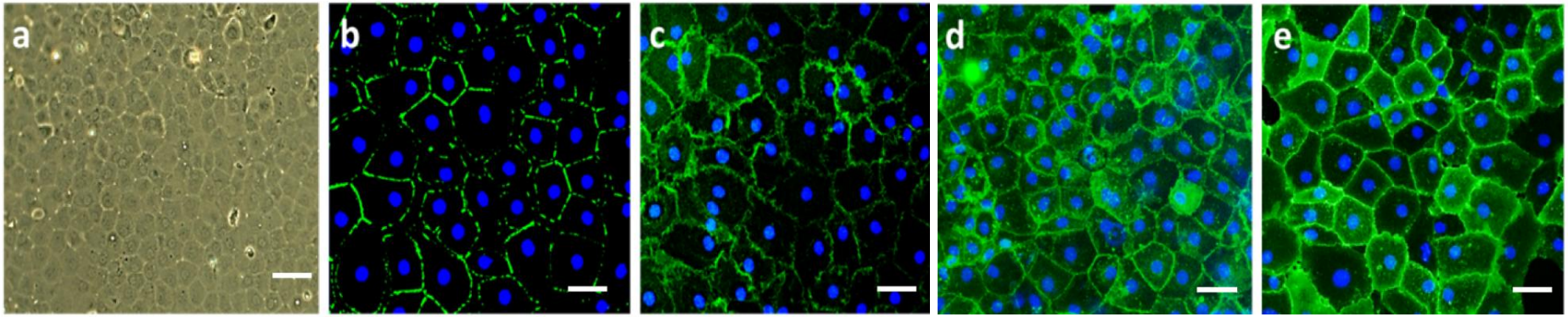
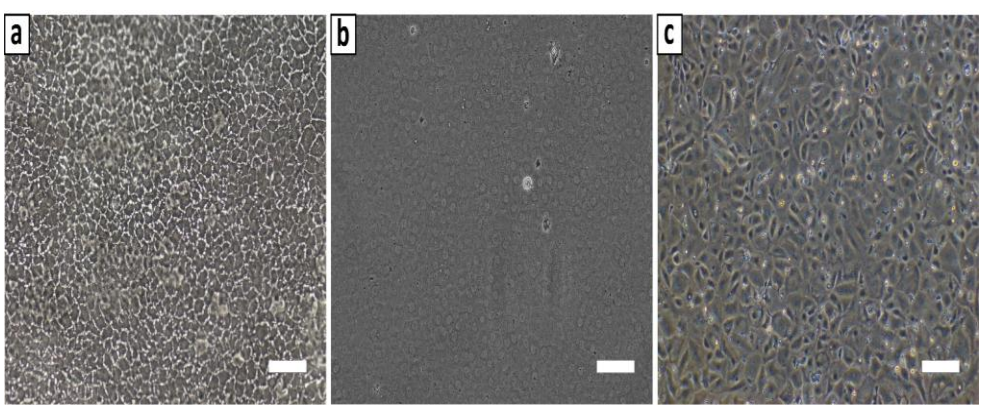
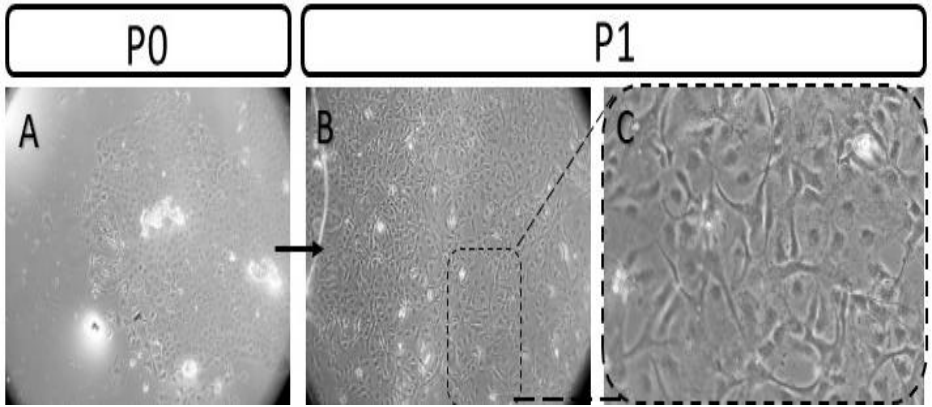


Figure 1. Overview of transplant strategies. Overview of the tissue engineering strategy (in blue) and the procured tissue strategy (in red). Abbreviations: GMP, Good Manufacturing Practice; QA, Quality Assurance; ALTK, Automated Lamellar Therapeutic Keratoplasty; EK, endothelial keratoplasty.
doi:10.1371/journal.pone.0100563.g001

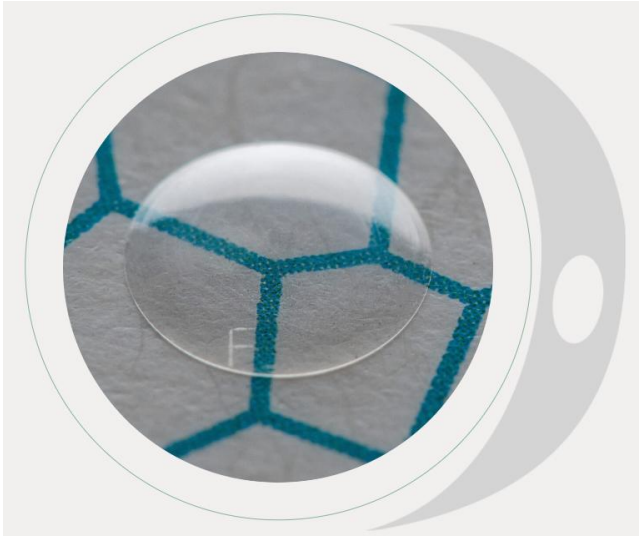


Human corneal endothelial cell culture from donor tissue. Phase contrast light microscope image showing typical hexagonal cell morphology (A). Immunofluorescence analysis shows the presence of zonula occludens-1 (ZO-1) (B), Na^+/K^+ ATPase (C), CD166 (D) and Prdx6 (E) expressed by primary corneal endothelial cells.





Human CECs in a corneal endothelium biopsy (A), primary cultured human CECs (B) and primary cultured CECs showing a characteristic morphological change experienced during primary expansion correlated with a cell loss of function and possible EMT (C). EMT after passage from P0 to P1?



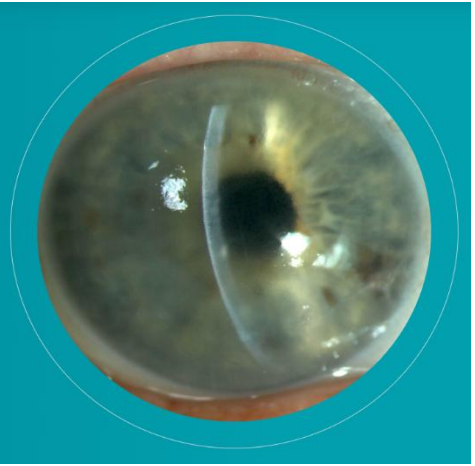
EndoArt®:

The future of corneal treatment

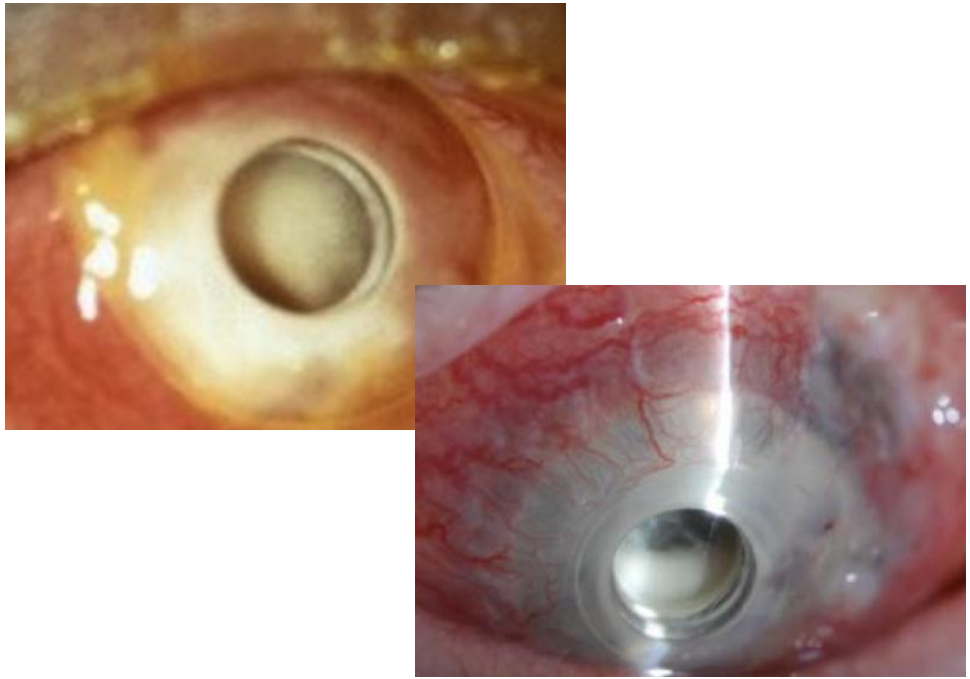
EndoArt® corneal artificial endothelial layer, is the first synthetic implant to treat corneal edema, saving vision and restoring function by creating a new type of corneal availability. EndoArt® attaches to the back of the corneal surface, preventing the transfer of fluids into the cornea and inhibiting the buildup of fluid that we know as edema. Performed via small incisions, the procedure is minimally invasive, preventing further injury to fragile eye tissue and encouraging a high degree of implantation success.
EndoArt® has demonstrated a substantial decrease in edema, improvement in vision, and reduction in pain in clinical studies, and it is CE- approved as well as in Israel (AMAR).

The Need

The human ocular endothelium can never regenerate. Therefore, any damage to the endothelium, including aging, results in corneal edema: a swelling of the eye's clear, dome-shaped outer surface. This affects millions of people around the world. Corneal edema causes pain and cloudy vision. If left untreated it can permanently damage the eye and affect sight. Current treatments for corneal edema depend on donated tissue. These transplants are often successful, but they are available only to those with access to human corneas. Meanwhile 13 million others experience first-hand the great shortage of donated corneas. They wait for human corneal transplants, in pain and with impaired vision, without an alternative solution.



Boston Keratoprosthesis



COMPLICATIONS!!!

65% Retroprosthetic Membrane

72% Glaucoma

19% Ret. Detachment

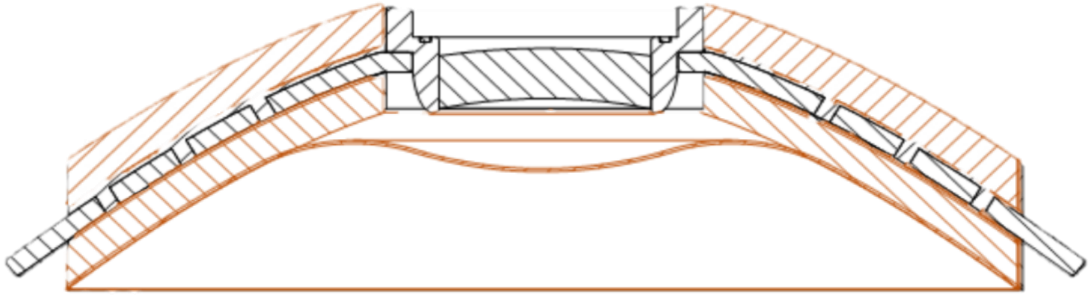
13% Endophthalmitis

HYBRID INTRACORNEAL DEVICE

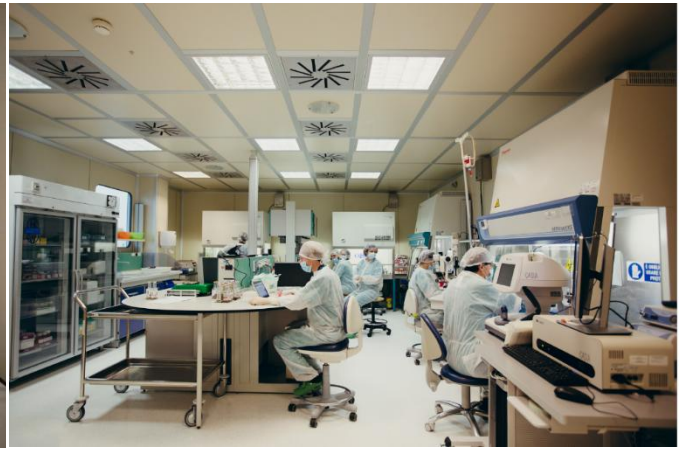
CORNEA TISSUE SCAFFOLD

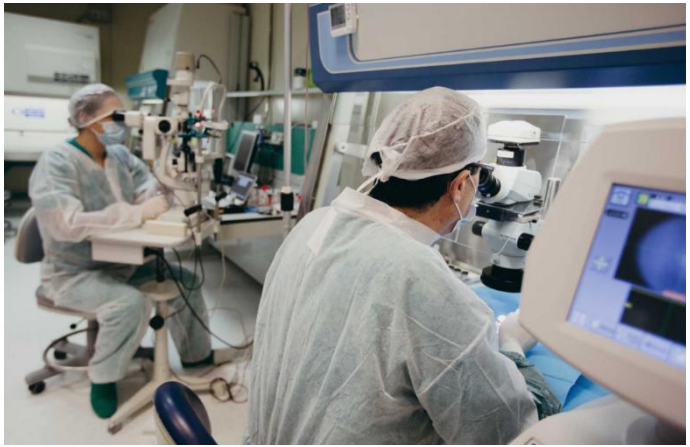
+

INTRACORNEAL PROSTHESIS

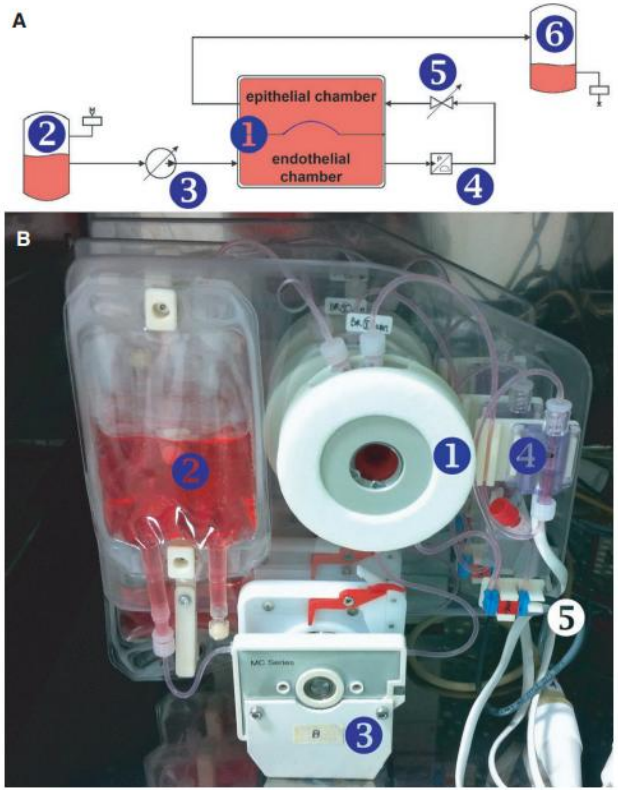


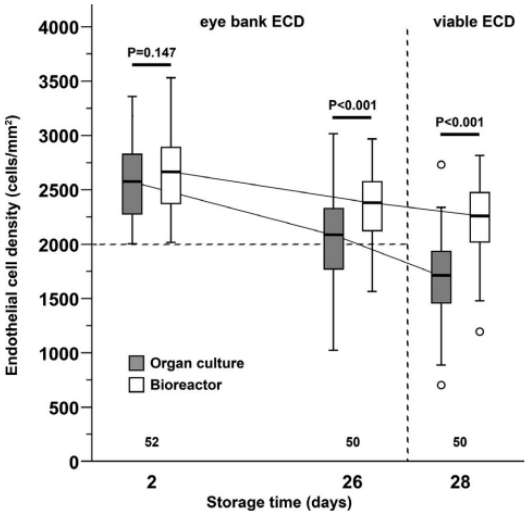
EYE BANKS IN THE FUTURE MIGHT LOOK DIFFERENT FROM TODAY AND USE NEWER TOOLS

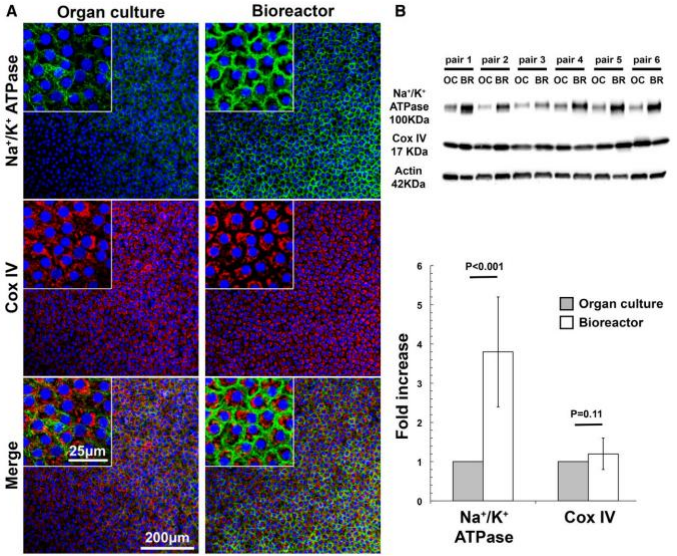




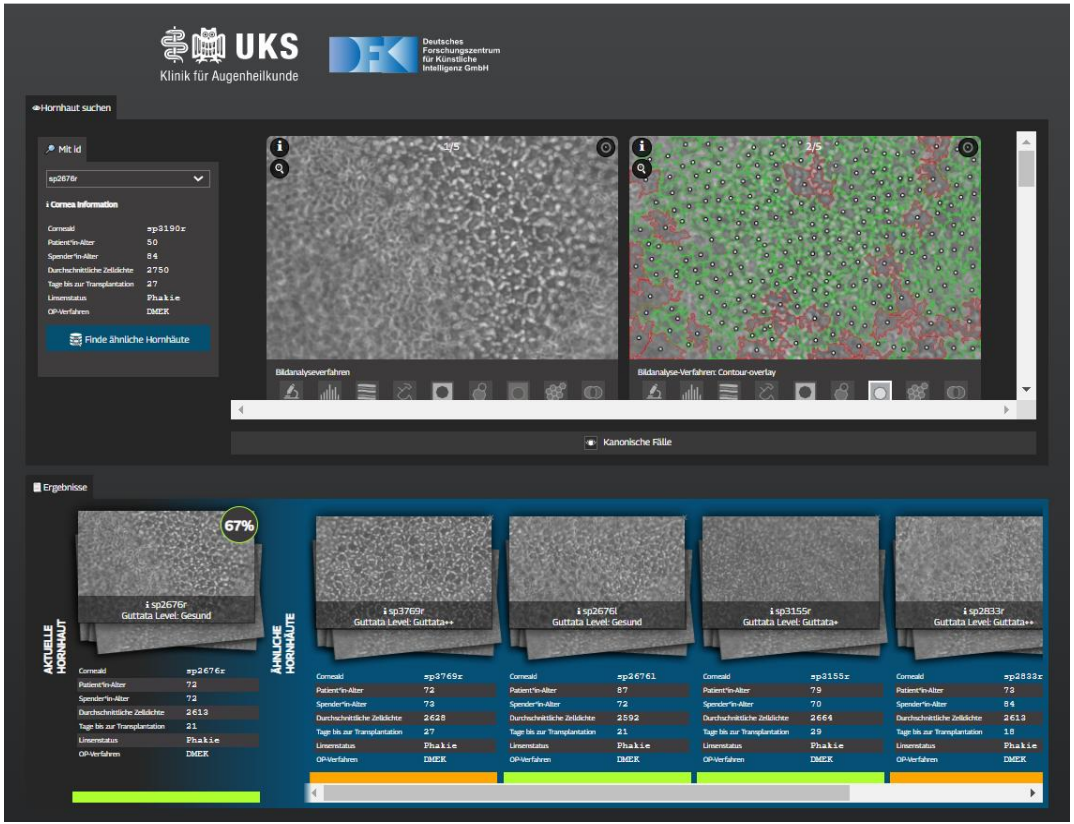
TOOLS TO HELP EYE BANKS (I): ACTIVE STORAGE MACHINE - corneas of better quality (↑ECD)







TOOLS TO HELP EYE BANKS (II): ARTIFICIAL INTELLIGENCE

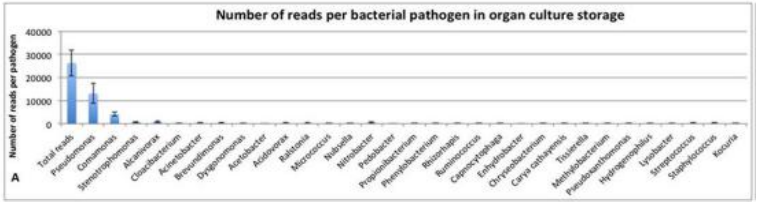


From: An artificial-intelligence-based decision support tool for the detection of Cornea guttata and the assessment of the donor corneas in the eye bank. Invest. Ophthalmol. Vis. Sci.. 2022;63(7):2756 – A0245.

BMJ Open Ophthalmology

Next-generation sequencing for the detection of microorganisms present in human donor corneal preservation medium

Mohit Parekh,[1,2] Davide Borroni,[3] Vito Romano,[3,4,5] Stephen B Kaye,[3] Davide Camposampiero,[2] Diego Ponzin,[2] Stefano Ferrari[2]



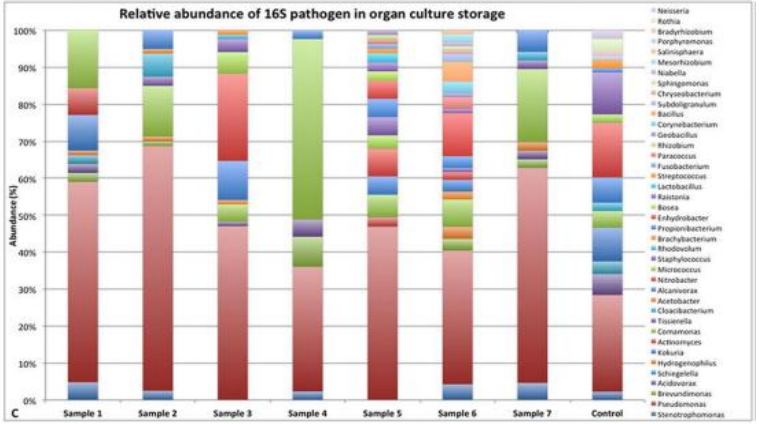


Table II

Total cost per batch and treatment, adjusted for failure rate (assumed 5%) and treatment yield per batch (post hoc adjustment).

	Facility A			Facility B		Facility C		Facility D
Case study	1	2	3	4	5	6	7	8
Materials	€15 171 (46%)	€12 801 (58%)	€11 897 (41%)	€35 096 (69%)	€13 916 (30%)	€12 542 (39%)	€6287 (28%)	€34 695 (19%)
Equipment	€5862 (18%)	€2506 (11%)	€904 (3%)	€2150 (4%)	€4063 (9%)	€7521 (23%)	€1604 (7%)	€12 247 (7%)
Personnel	€9202 (28%)	€ 4997 (23%)	€9747 (33%)	€9384 (18%)	€15 296 (33%)	€8147 (25%)	€10 754 (47%)	€35 723 (20%)
Facility	€2801 (8%)	€1632 (7%)	€6674 (23%)	€4496 (9%)	€13 162 (28%)	€4167 (13%)	€4,167(18%)	€99 047 (54%)
Total/batch	€33 036	€21 936	€29 221	€51 126	€46 437	€32 376	€22 812	€181 713
Fixed	€4206 (13%)	€4,206 (19%)	€4,206 (14%)	€ 9389 (18%	€18 908 (41%)	€5419 (17%)	€5598 (25%)	€81 958 (45%)
Variable	€28 830 (87%)	€17 730 (81%)	€25 016 (86%)	€41 738 (82%)	€27 529 (59%)	€26 957(83%)	€17 214 (75%)	€99 756 (55%)
Failure rate adjustment								
Failure rate	5%	5%	5%	5%	5%	5%	5%	5%
Total/batch	€34 688	€23 033	€30 682	€53 683	€48 759	€33 995	€23 952	€190,799
Fixed	€4416 (13%)	€4416 (19%)	€4416 (14%)	€9858 (18%)	€19 854 (41%)	€5690 (17%)	€5877 (25%)	€86,055 (45%)
Variable	€30 272 (87%)	€ 18 617 (81%)	€26 266 (86%)	€43 825 (82%)	€28 905 (59%)	€28 305 (83%)	€18 075 (75%)	€104 743 (55%)
Post hoc adjustment								
Treatment yield/batch	1	1	1	1	1	1	1	22
Total/treatment	NA	NA	NA	NA	NA	NA	NA	€8673
Fixed	NA	NA	NA	NA	NA	NA	NA	€3912
Variable	NA	NA	NA	NA	NA	NA	NA	€4761

Total costs are presented in fixed and variable cost, €(%). One treatment can consist of more than one dose.

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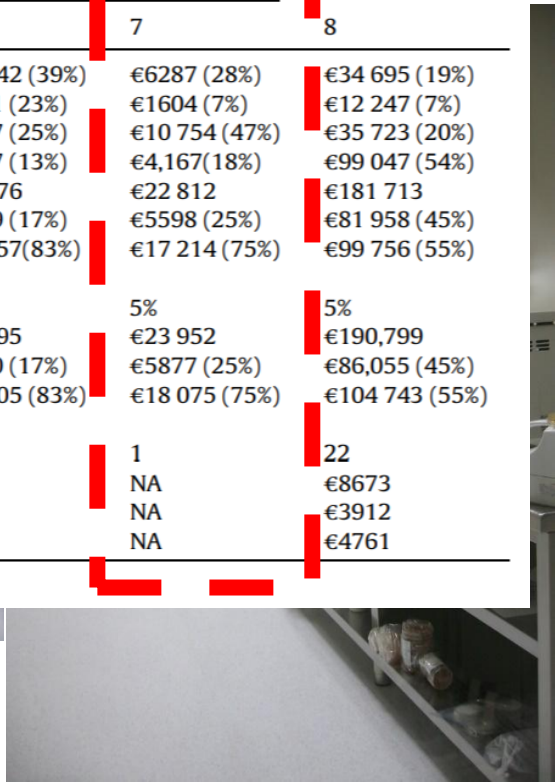
FULL-LENGTH ARTICLE

Manufacturing

What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings



Conclusioni: *eye banking* 2.0

- Diminuita dipendenza dalle donazioni
- Aumento dell'automazione nella selezione e lavorazione di donatori e tessuti
- Cambiamento nelle lavorazioni:
  - ✓ Da tessuti a cellule
  - ✓ Tessuti ibridi (tessuto + dispositivo)
- Da eye banking a oftalmologia rigenerativa