XVIII CORSO NAZIONALE SIBO 2026

MILAN, June 6th 2026

Trapianto di cellule endoteliali e colture cellulari, la ricerca in banca

Stefano Ferrari

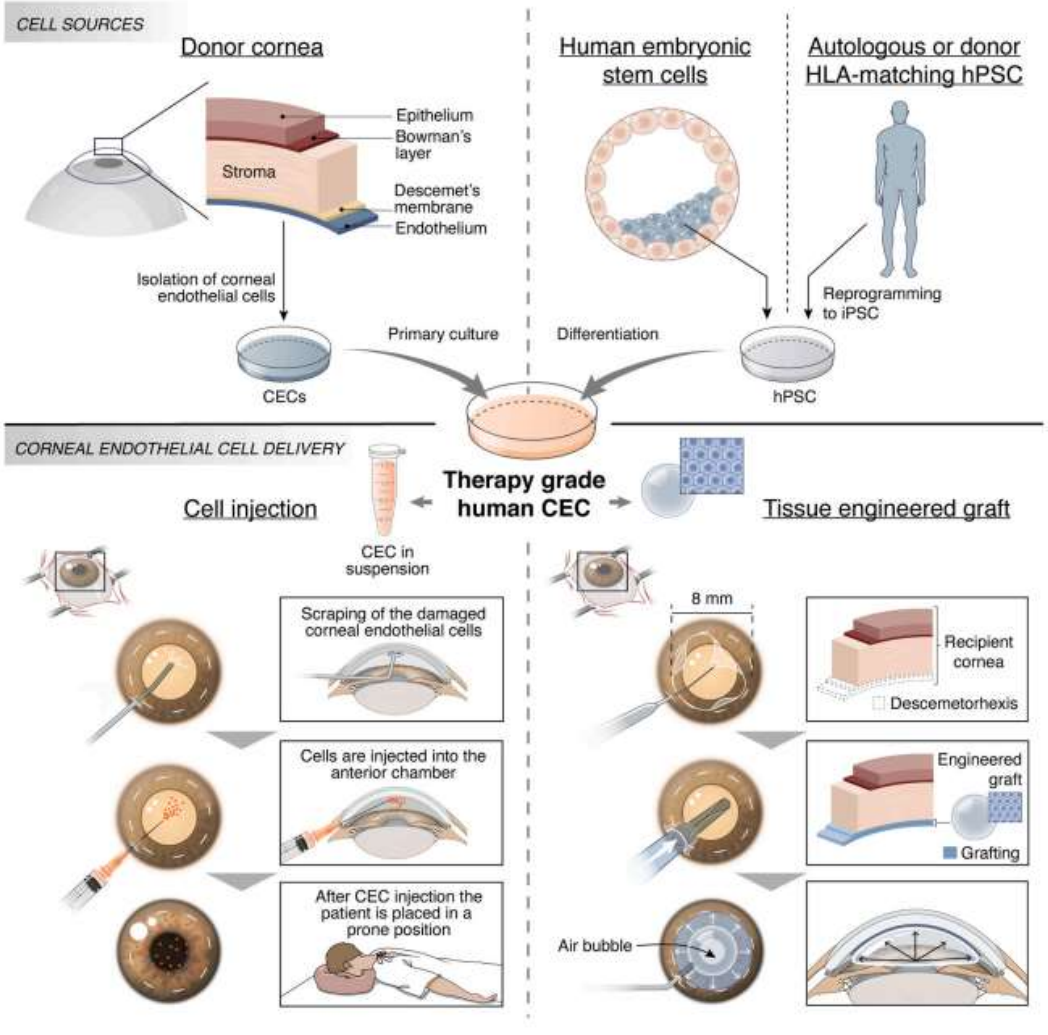
Fondazione Banca degli Occhi del Veneto ETS - stefano.ferrari@fbov.it
Università degli Studi di Ferrara - stefano.ferrari@unife.it

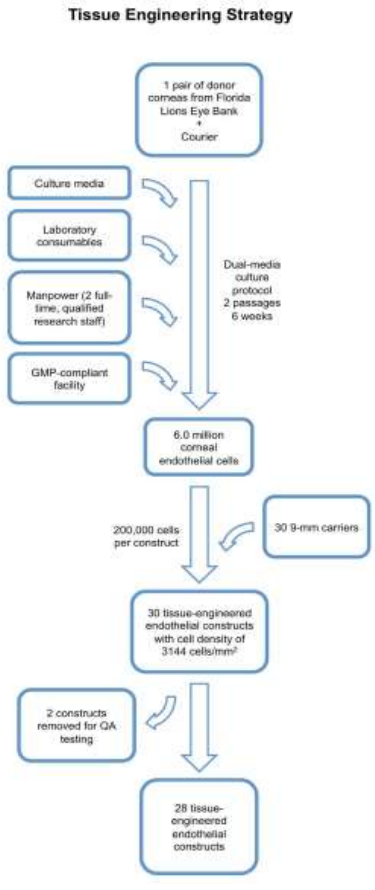
DISCLOSURE STATEMENT

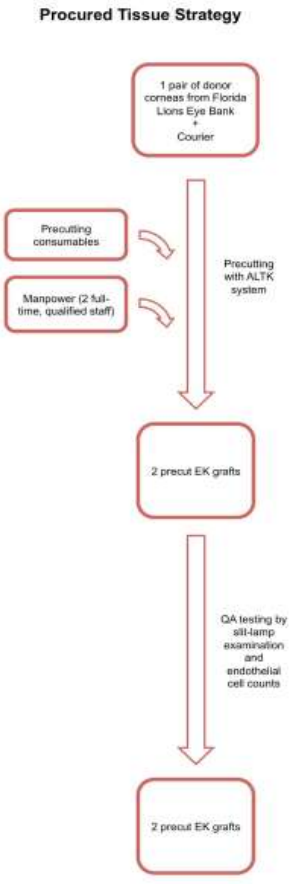
Stefano Ferrari is an employee of *Fondazione Banca degli Occhi del Veneto ETS* (The Veneto Eye Bank Foundation), a non profit, social welfare organization and regional centre of reference for cornea transplantation and research into epithelial stem cells.

Since October 2025, Stefano Ferrari has been appointed as *Professore Straordinario* at the *Dipartimento di Medicina Traslazionale e per la Romagna* of the University of Ferrara.

I have no commercial interests to disclose

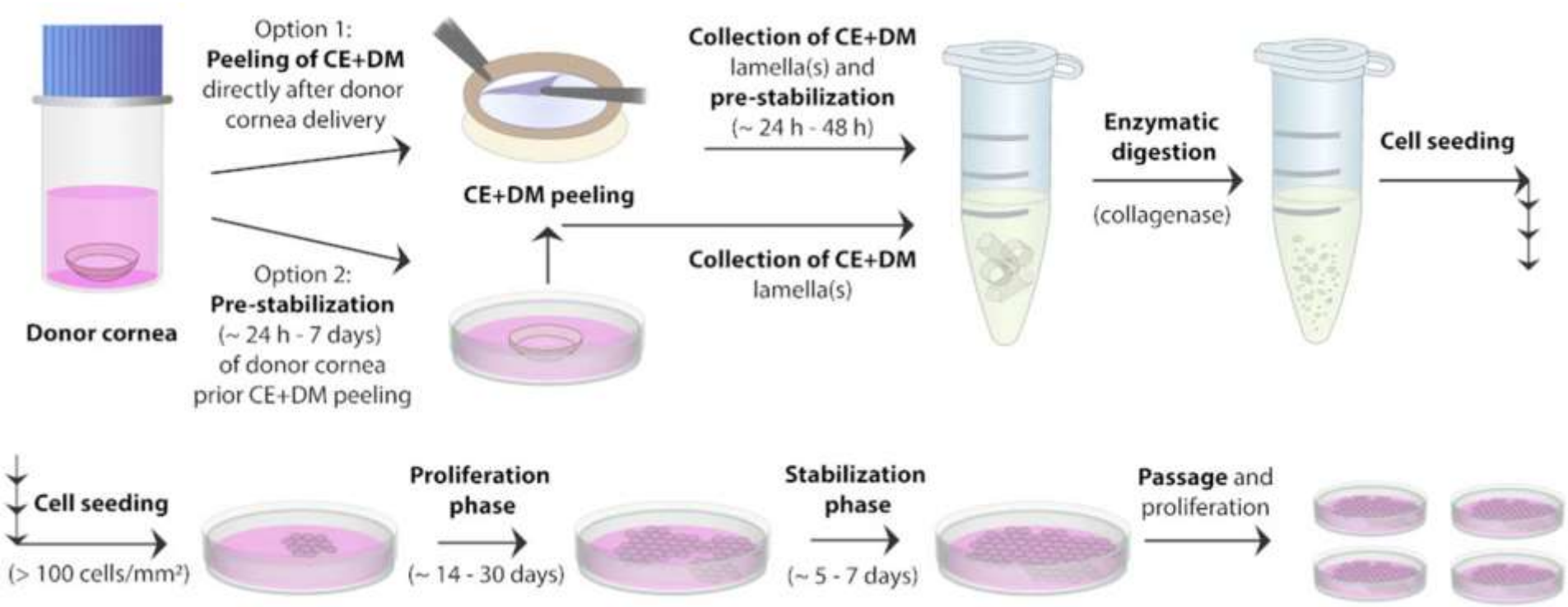


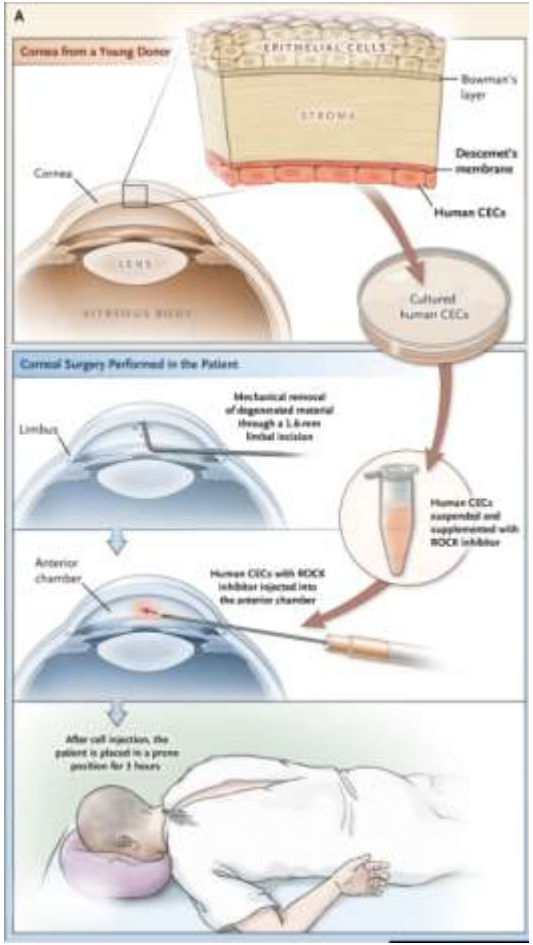




FONDAZIONE BANCA DEGLI OCCHI DEL VENETO - ETS

HOW CELLS ARE ISOLATED AND CULTURED





AMERICAN ACADEMY OF OPHTHALMOLOGY®

Five-Year Follow-up of First 11 Patients Undergoing Injection of Cultured Corneal Endothelial Cells for Corneal Endothelial Failure

Kohsaku Numa, MD,[1] Kojiro Imai, MD, PhD,[1] Morio Ueno, MD, PhD,[1] Koji Kitazawa, MD, PhD,[1] Hiroshi Tanaka, MD, PhD,[1] John D. Bush, BA,[1] Satoshi Teramukai, PhD,[2] Naoki Okumura, MD, PhD,[3] Noriko Koizumi, MD, PhD,[3] Junji Hamuro, PhD,[1] Chie Sotozono, MD, PhD,[1] Shigeru Kinoshita, MD, PhD[4]

Purpose: To report the safety and efficacy of a novel cell injection therapy using cultured human corneal endothelial cells (hCECs) for endothelial failure conditions via the report of the long-term 5-year postoperative clinical data from a first-in-humans clinical trial group.

Design: Prospective observational study.

Participants: This study involved 11 eyes of 11 patients with pseudophakic endothelial failure conditions who underwent hCEC injection therapy between December 2013 and December 2014.

Methods: All patients underwent follow-up examinations at 1 week, 4 weeks, 12 weeks, and 24 weeks and 1 year, 2 years, 3 years, 4 years, and 5 years after surgery. Specific corneal endothelial cell parameters (i.e., corneal endothelial cell density [ECD], coefficient of variation of area, and percentage of hexagonal cells) and central corneal thickness, best-corrected visual acuity (BCVA) on a Landolt C eye chart, and intraocular pressure (IOP) were recorded.

Main Outcome Measures: The primary outcome was the change in central ECD after cell injection therapy, and the secondary outcome was corneal thickness, BCVA, and IOP during the 5-year-postoperative follow-up period.

Results: At 5 years after surgery, normal corneal endothelial function was restored in 10 of the 11 eyes, the mean ± standard deviation central corneal ECD was 1257 ± 467 cells/mm^2 (range, 601−2067 cells/mm^2), BCVA improved significantly in 10 treated eyes, the mean visual acuity changed from 0.876 logarithm of the minimum angle of resolution before surgery to 0.046 logarithm of the minimum angle of resolution after surgery, and no major adverse reactions directly related to the hCEC injection therapy were observed.

Conclusions: The findings in this study confirmed the safety and efficacy of cultured hCEC injection therapy for up to 5 years after surgery. *Ophthalmology 2021;128:504-514 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

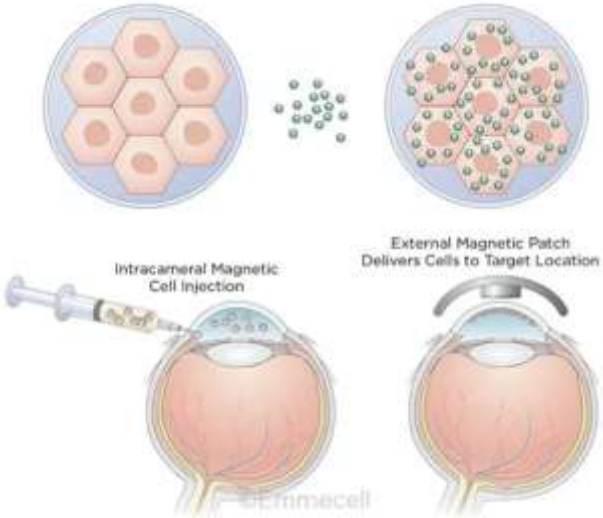
Product/ Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Approved	Next Anticipated Milestone
Vyznova	Bullous keratopathy of the cornea	Approved (Japan)					Commercial Launch 2H 2024
AURN001	Corneal edema secondary to corneal endothelial dysfunction		Phase 3 (U.S.) *				Twelve-month topline results from U.S. Phase 2 trial in 2H 2025
Cryopreserved formulation**	Corneal edema secondary to corneal endothelial dysfunction			Phase 2			Twelve-month topline results from pilot clinical trial in Q1 2026

Study of Safety and Tolerability of EO2002 in the Treatment of Corneal Edema

ClinicalTrials.gov ID NCT04894110

Sponsor Emmecell

Information provided by Emmecell (Responsible Party)



EMMECELL

Emmecell Completes Last Patient Last Visit for Proof-of-Concept Trial of Groundbreaking Cell Therapy for Corneal Edema

MENLO PARK, Calif., Oct. 8, 2024 /PRNewswire/ -- Emmetrope Ophthalmics, LLC ("Emmecell"), a clinical-stage biotechnology company pioneering the discovery and development of cell-based therapies for the treatment of serious eye diseases, today announced the successful completion of the last patient last visit in its phase 1 extension study EMME-001, a 21-patient randomized, double-masked, US based, multi-center trial assessing the safety and efficacy of EO2002 for the treatment of corneal edema. This milestone marks a significant step forward in the development of an advanced treatment option aimed at improving visual function for patients suffering from Fuchs dystrophy, pseudophakic bullous keratopathy, and other causes of corneal edema.

In the cohort receiving 150,000 endothelial cells, patients experienced an impressive **mean gain of 11 letters in Best Corrected Visual Acuity (BCVA)** at six months. Notably, **38% of patients achieved a vision gain of at least 15 letters**, a crucial regulatory milestone. Across all dose levels tested—150,000, 500,000, and 1 million cells—participants showed improvement in BCVA and reductions in central corneal thickness (CCT), reflecting the therapy's broad efficacy.

CHALLENGES IN CELL EXPANSION

First in vitro culture protocol: 1965

Limited Proliferation

Species-dependent: rabbits >> rodents > dogs >> primates/humans

Endothelial-to-Mesenchymal Transition (EMT)

Loss of hexagonal morphology, tight junctions, and pump function

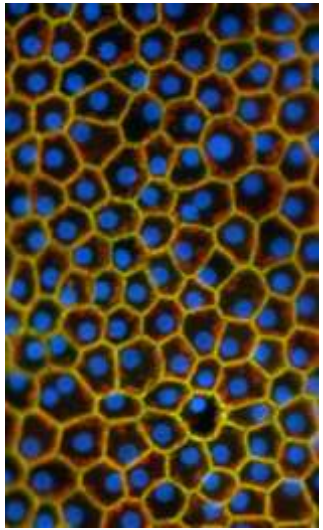
Age-Dependent Constraints

Replicative senescence limits expansion potential

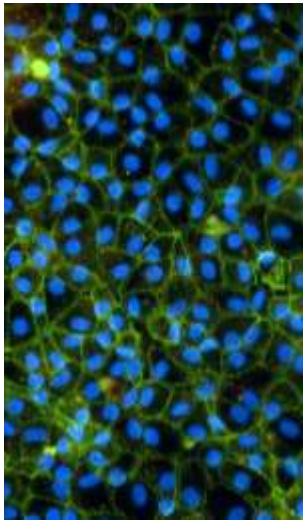
Culture Conditions

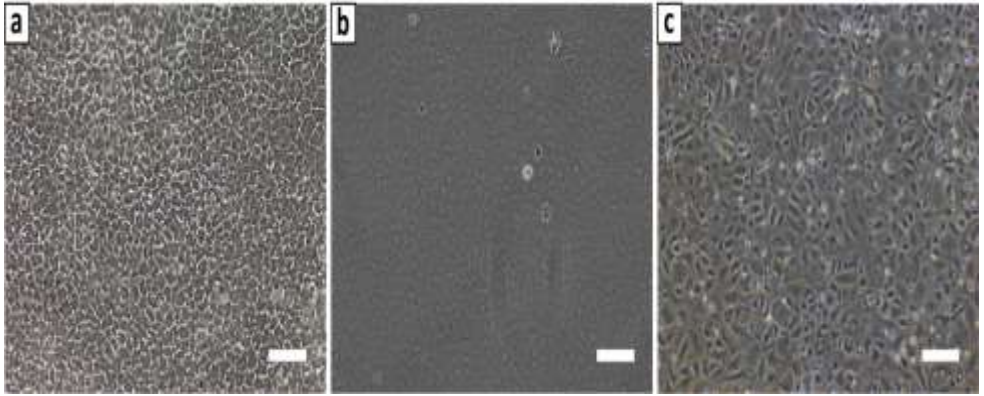
Excessive mitogens, TGF-β, low density, non-physiological stiffness

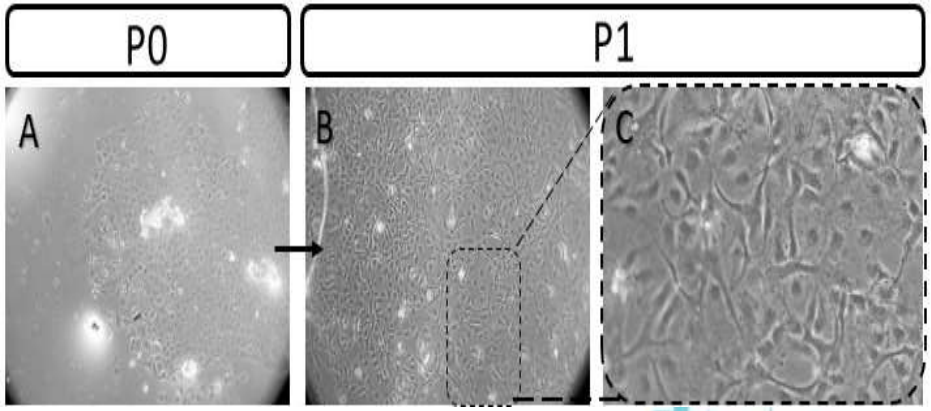
Result: Limited clinical translation for decades



ENDOTHELIAL TO MESENCHYMAL TRANSITION (EMT)







Cell Reports Medicine

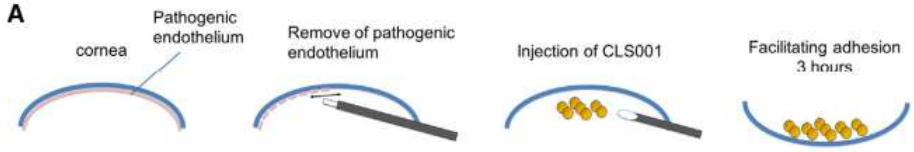
CELLUSION

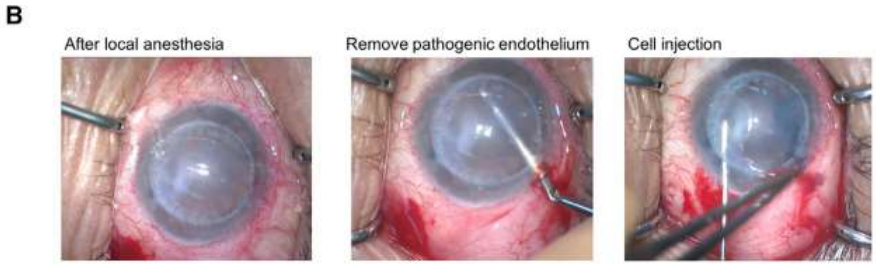
Report

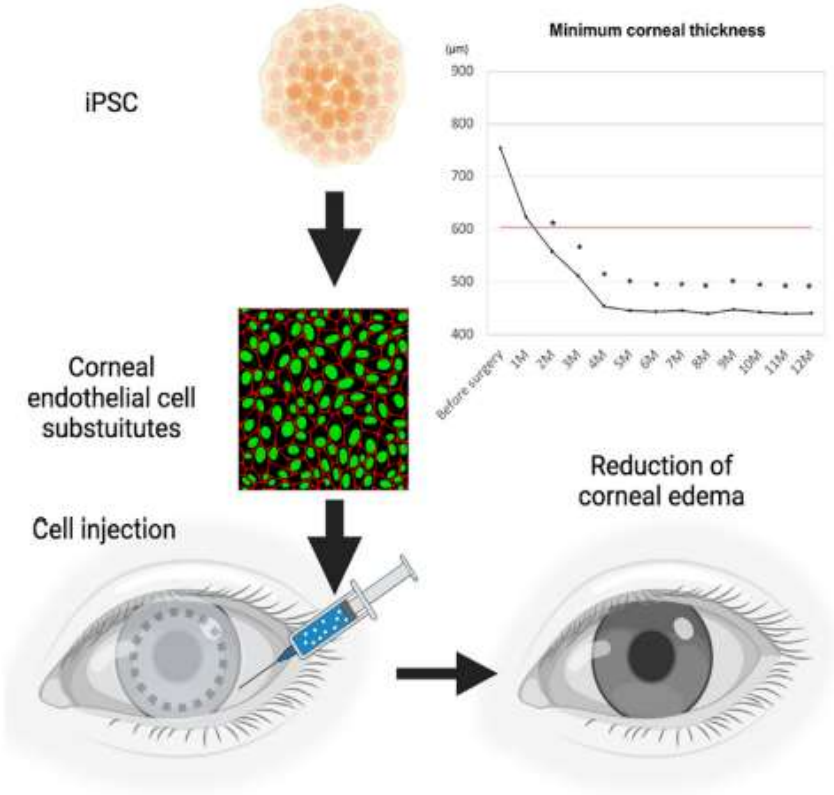
A first-in-human clinical study of an allogenic iPSC-derived corneal endothelial cell substitute transplantation for bullous keratopathy

Masatoshi Hirayama,[1,4] Shin Hatou,[1,2,3] Masaki Nomura,[3] Risa Hokama,[1] Osama Ibrahim Hirayama,[1] Emi Inagaki,[1,4] Kumi Aso,[1] Tomoko Sayano,[1,2] Hiromi Dohi,[1] Tadaaki Hanatani,[3] Naoko Takasu,[5] Hideyuki Okano,[4] Kazuno Negishi,[1] and Shigeto Shimmura[1,6,7,*]

[1]Department of Ophthalmology, Keio University School of Medicine, Shinjuku-ku 160-8582, Tokyo, Japan
[2]Cellusion Inc., Chuo-ku, Tokyo 103-0024, Japan
[3]CiRA Foundation, Sakyo-ku, Kyoto 606-8397, Japan
[4]Department of Physiology, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan
[5]Department of Clinical Regenerative Medicine, Fujita Medical Innovation Center, Fujita Health University, Ota-ku, Tokyo 144-0041, Japan







Slide from Stefano Ferrari

Advanced Therapy Medicinal Products require GMP standards:

- regulatory issues
- high costs
- lenghty procedures

Simple
Non cultured
Endothelial
Cells

Preparation

Donor cornea
Endothelial Cell Density
< 2,500 cell/mm²

Peeled Descemet Membrane
incubated in M5-Endo Medium
[48h]

Endothelial Cells Isolation

TrypLE Select 1x [30-50min]

Corneal Endothelial Cells, Clusters,
Descemet Membrane debris

Pre-wet
100 µm filter

Pure Single Corneal Endothelial Cells

Patient

Treatment

Corneal Endothelial Cell Injection

Suspension
Single Corneal Endothelial Cells + M5-Endo Medium + 10 µM ROCKi

Ventral position [3h]

30-G silicone canula

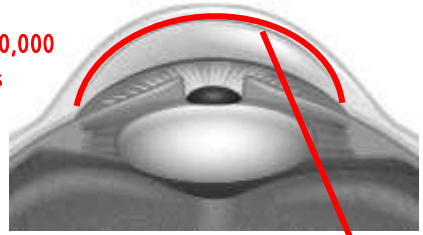
Descemet Membrane Decellularization

Pool of cells from 2 corneas from old donors with ECD<2,000/mm²

for

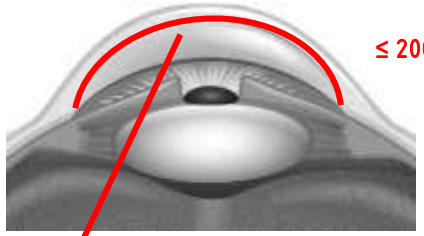
1 recipient (to obtain ECD >2,000/mm²)

Endothelial area 1 cm2 ≈ ↓ ≤ 200,000 cells



OLD DONOR with LOW ECD

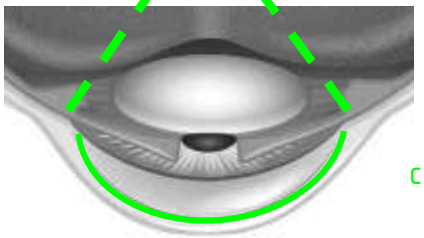
Endothelial area 1 cm2 ≈ ↓ ≤ 200,000 cells



OLD DONOR with LOW ECD

Direct cell injection without previous cell culture.

≈ 3 weeks of culture.



> 2,000 cells/mm²

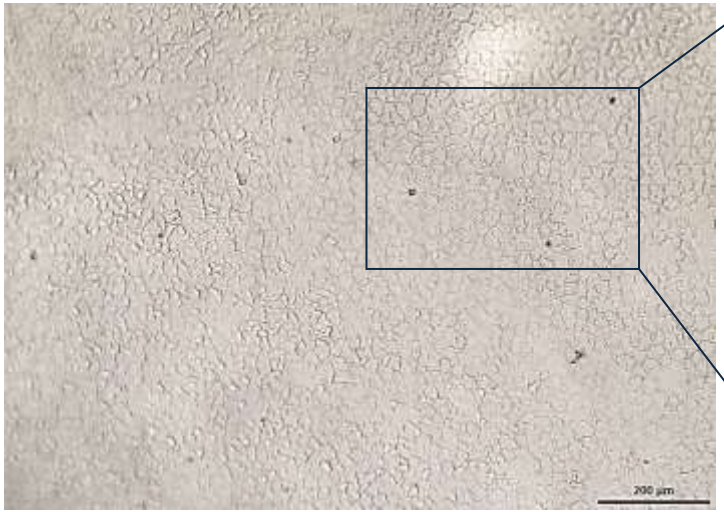
1 cm ≈ Φ → 1 cm2 ≈ area

On cornea +DM

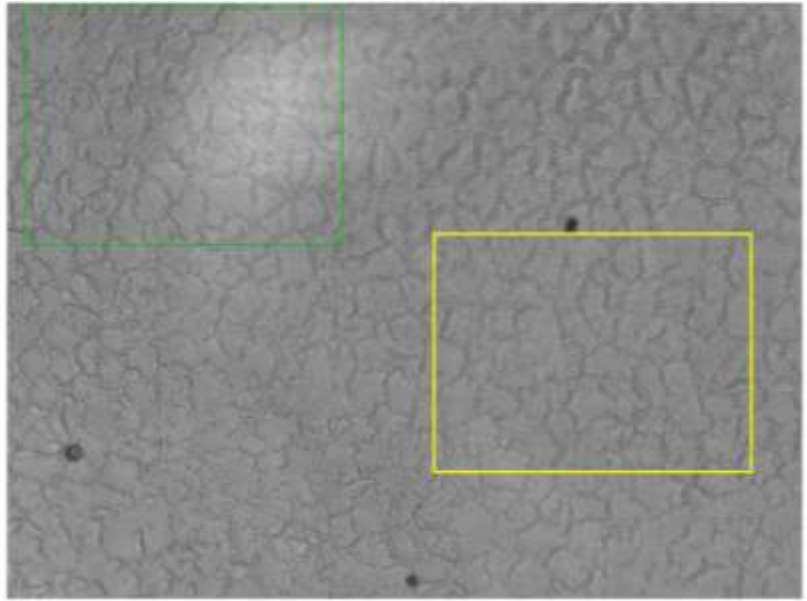
On cornea −DM

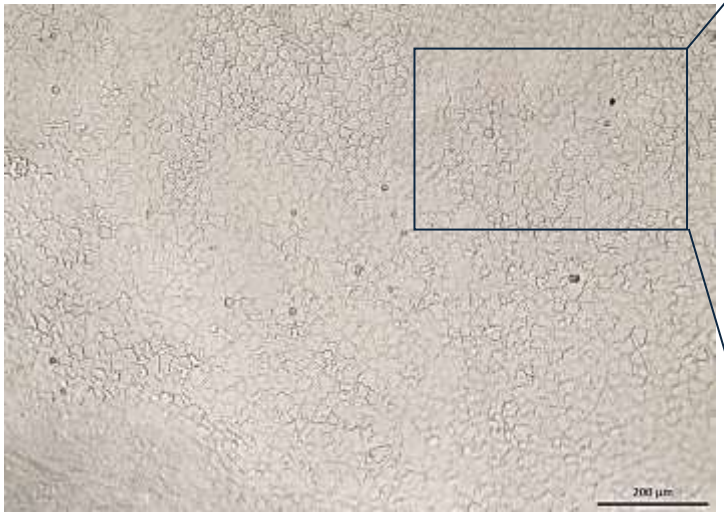
Evaluation corneal endothelium – Donor 1

Pre treatment


200 µm

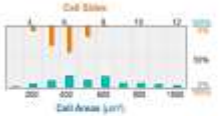

Multi-Sample Average
CD 1.701
CV 44
HEX % 40
SD 257
Total Area µm² 38.796
Total Num 66
Cell Sizes
Cell Area (µm²)
1.538 CD 1.838
44 CV 42
37 % HEX % 43
286 SD 228
650 µm² Ave µm² 544
27 Num 39





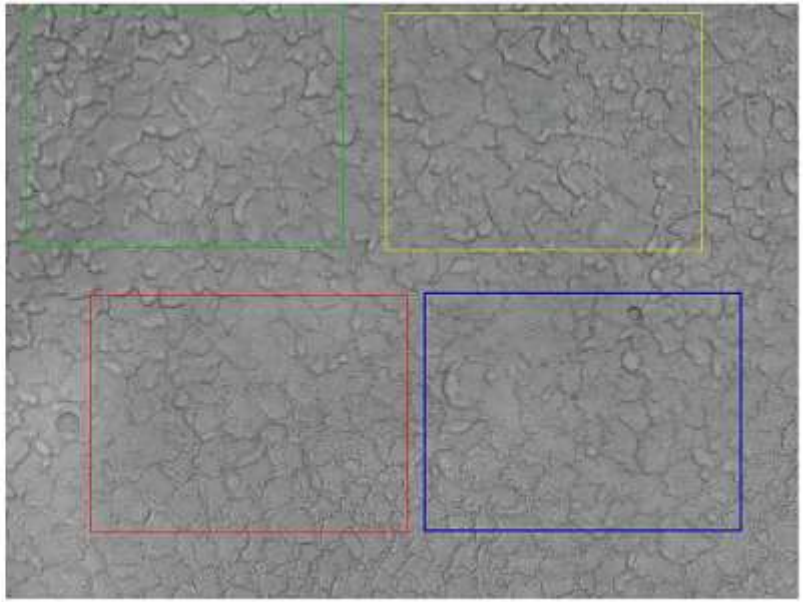
Multi-Sample Average

CD	1.698
CV	41
HEX	42
SD	243
Total Area	75.974
Total Num	129



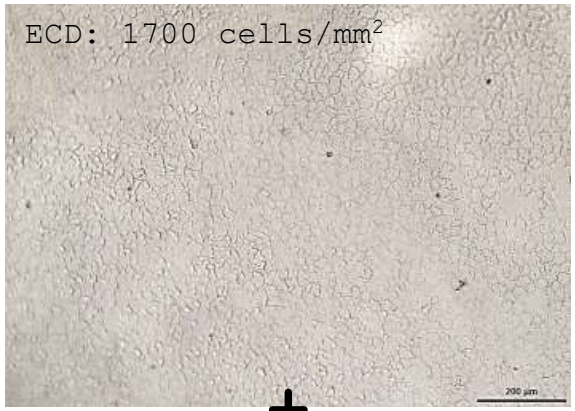
1.751	CD	1.890
41	CV	37
40	HEX	45
236	SD	196
571	Ave	529
37	Num	37

1.698	CD	1.399
40	CV	41
40	HEX	43
238	SD	294
589	Ave	715
32	Num	23



Evaluation corneal endothelium

Pre treatment



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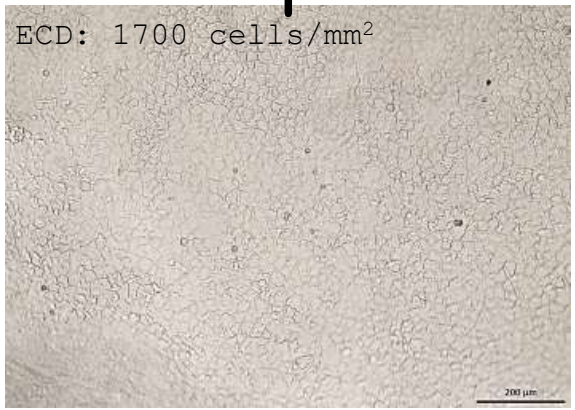
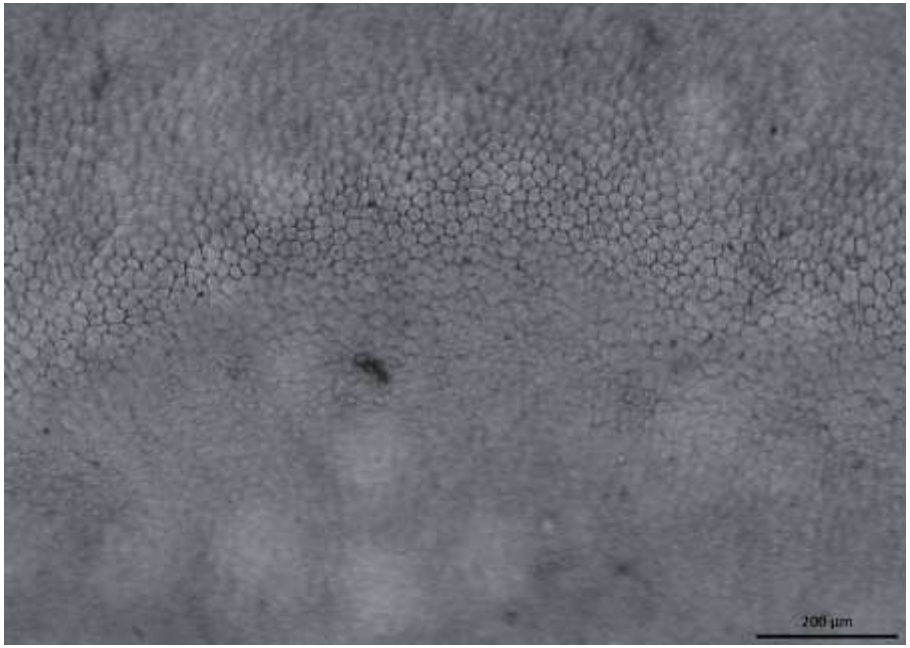
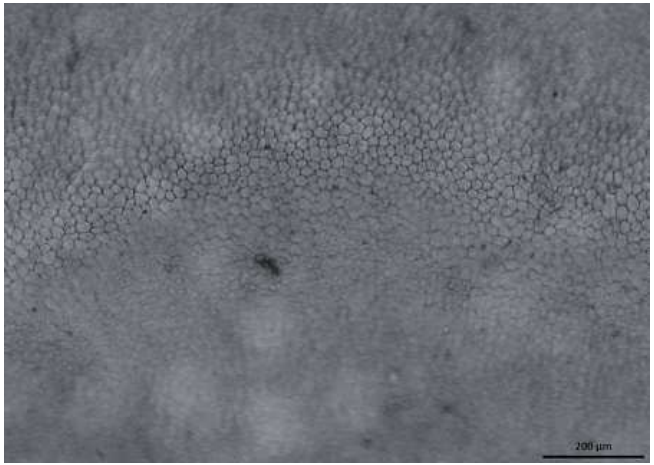
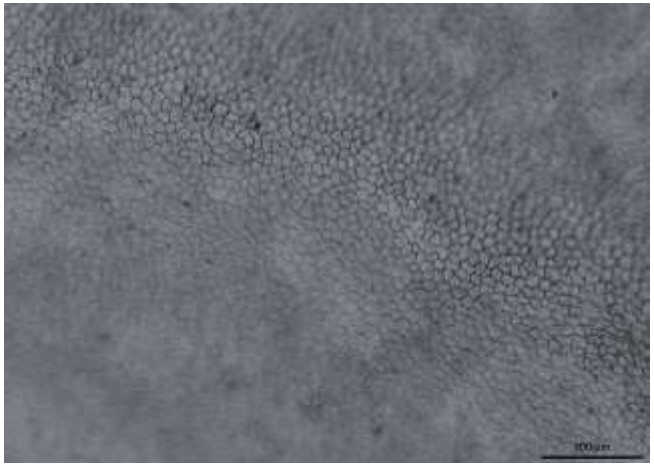
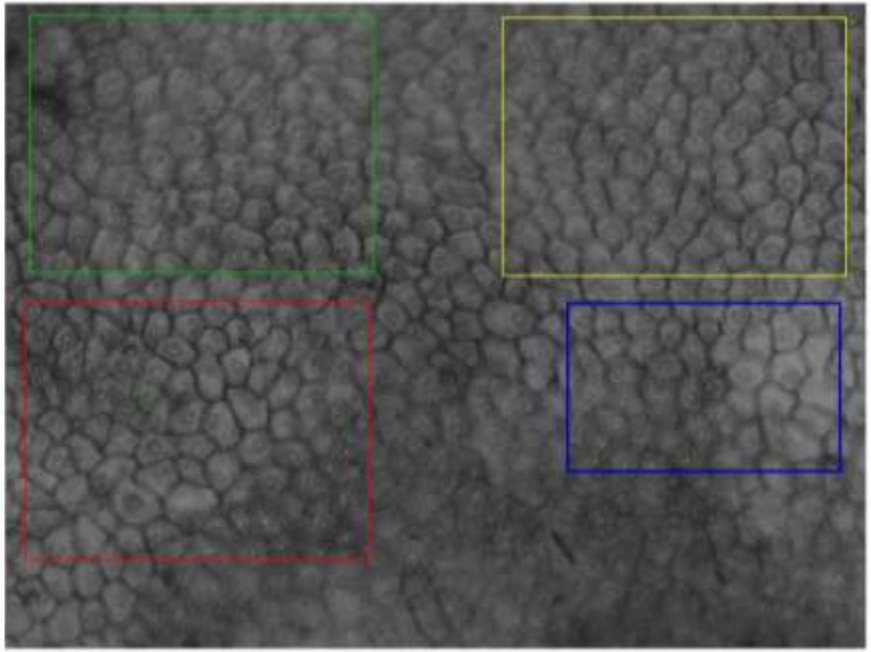


Post treatment – one month later





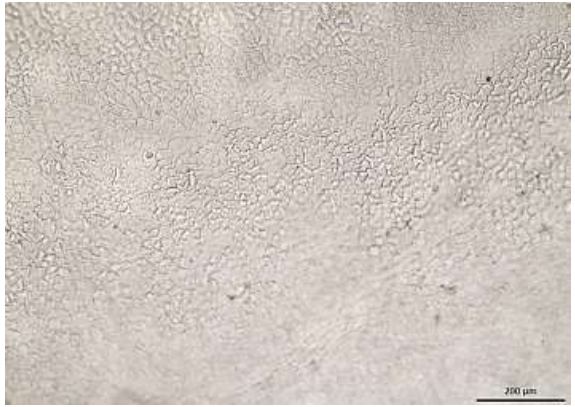




Gold standard: CV < 50% and HEX > 50% (Gasser et al., 2015)

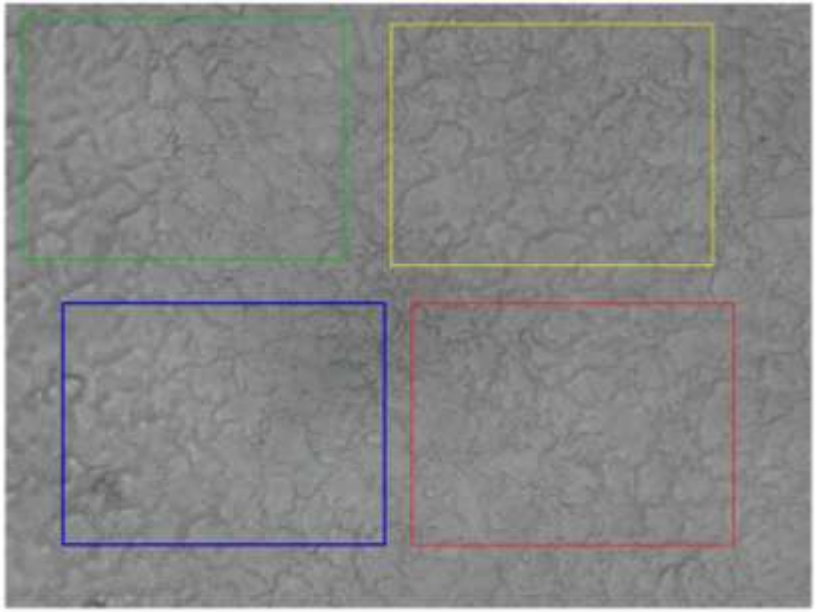
Evaluation corneal endothelium – Donor 2

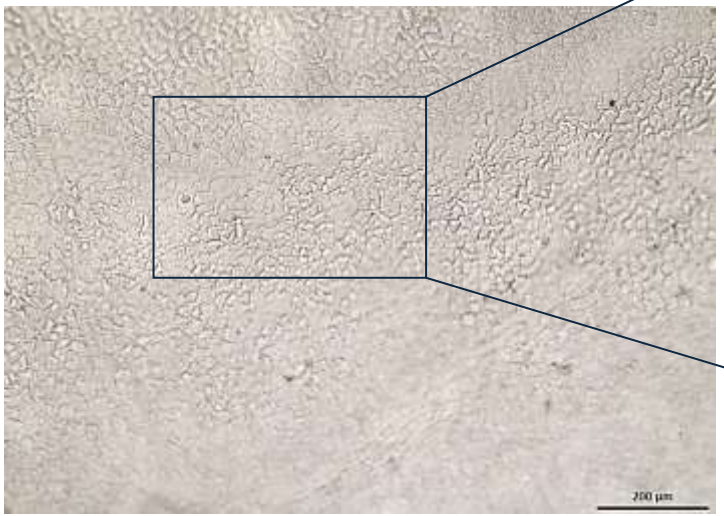
Pre treatment



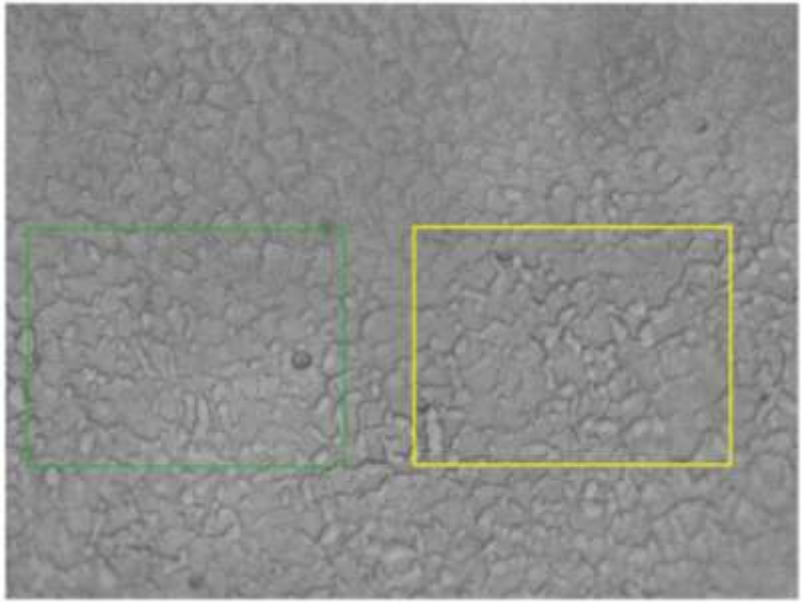

200 µm


Multi-Sample Average
CD 1.527
CV 44
HEX % 36
SD 291
Total Area µm² 72.013
Total Num 110
1.437 CD 1.536
43 CV 42
32 % HEX % 34
297 SD 276
696 µm² Axis µm² 651
25 Num 32
1.396 CD 1.736
46 CV 46
26 % HEX % 50
330 SD 264
717 µm² Axis µm² 576
23 Num 30



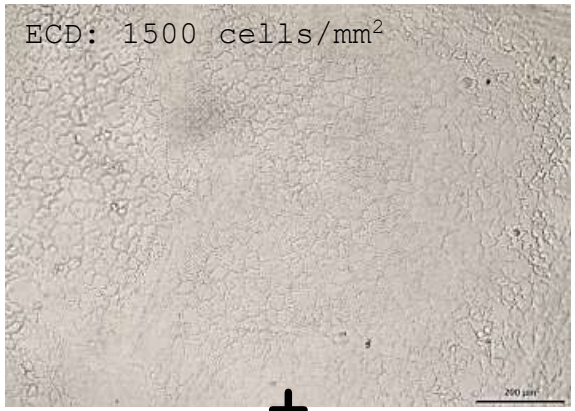

200 µm


Multi-Sample Average
CD 1.779
CV 45
HEX 43
SD 264
Total Area 37.676
Total Num 67
1.908 CD 1.653
39 CV 49
40 HEX 46
202 SD 299
524 Ave 605
35 Num 32



Evaluation corneal endothelium

Pre treatment



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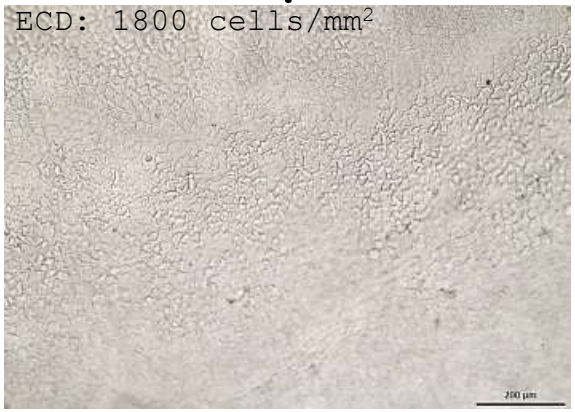
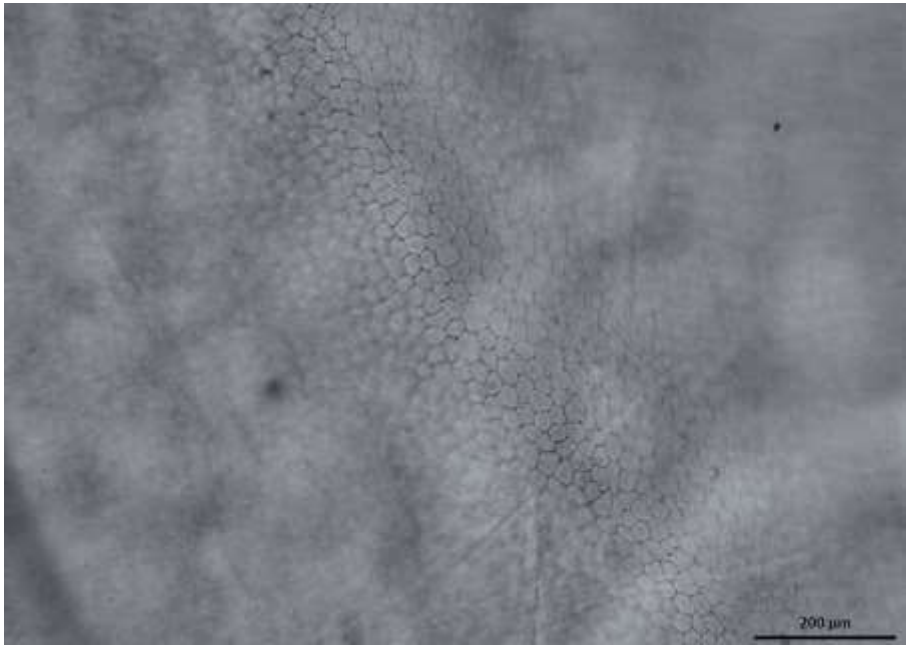
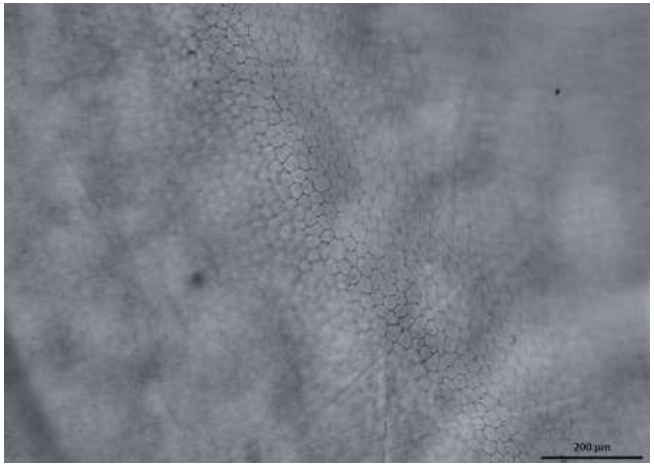
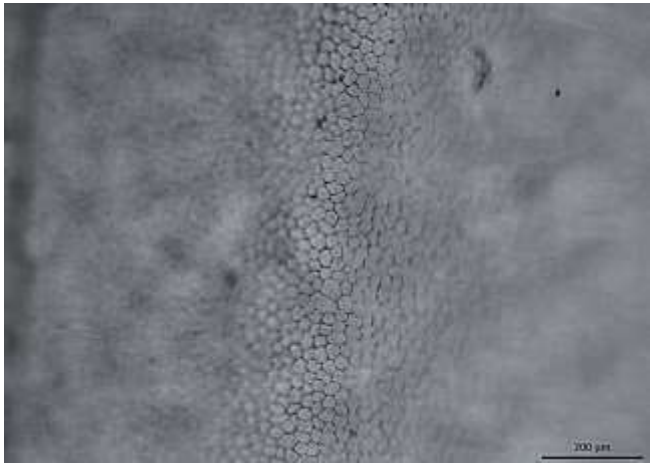
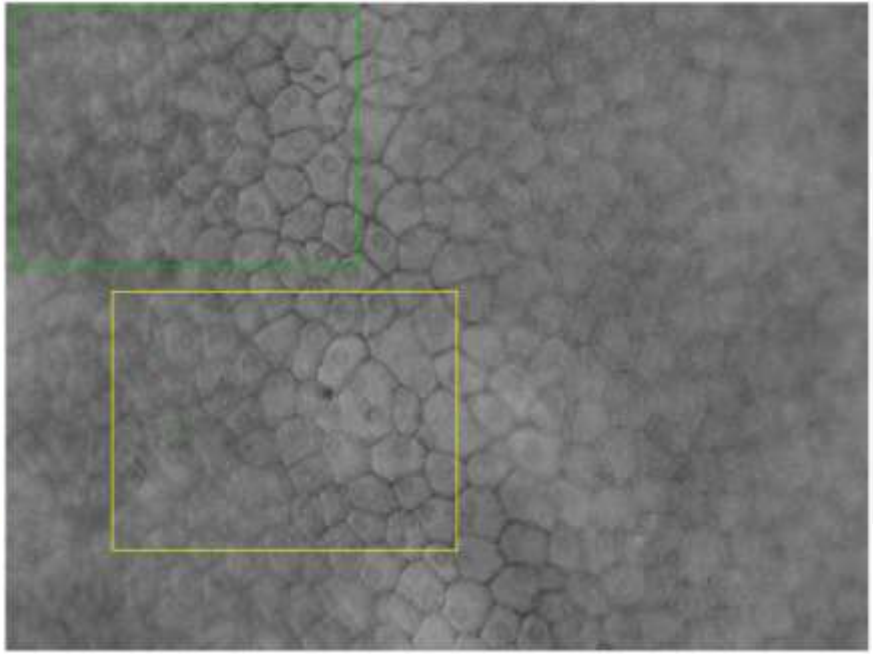


Post treatment – one month later







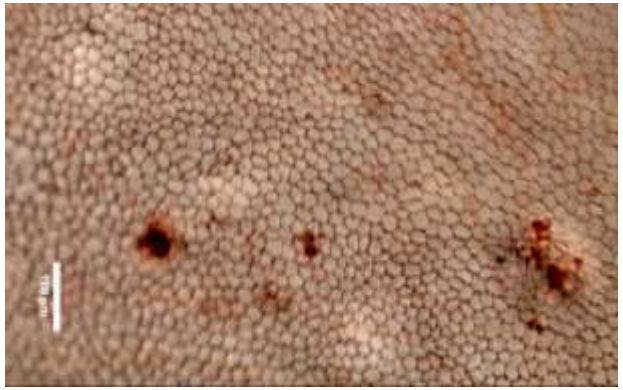


Gold standard: CV < 50% and HEX > 50% (Gasser et al., 2015)

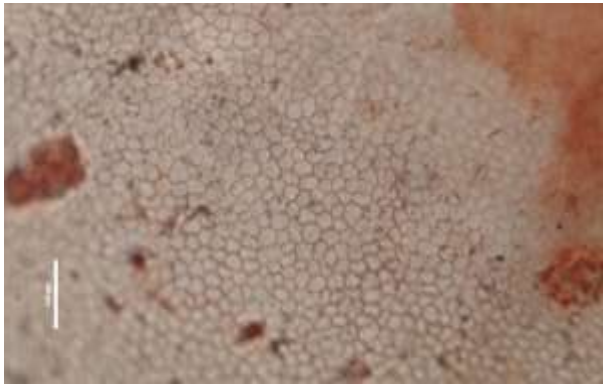
Alizarin Red staining

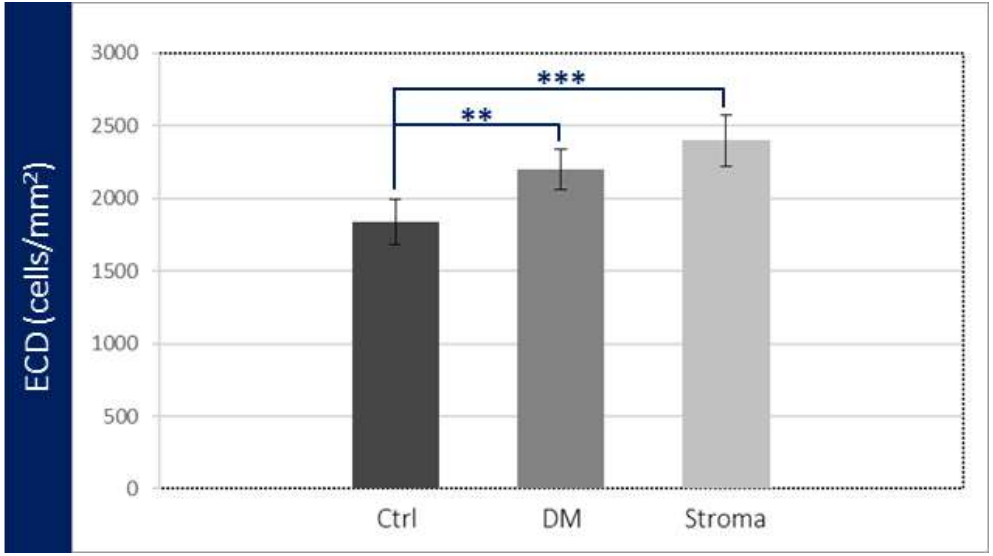
Control

+DM



Stroma





Simulation of bullous keratopathy: removal of just the endothelial cells

	ECD (cells/mm²)	CV (%)	HEX (%)
Donor 1 OD	1800	45	43
Donor 1 OS	1500	44	36
Recipient 1	**2000**	**40**	**56**
Donor 2 OD	1700	44	40
Donor 2 OS	1700	41	42
Recipient 2	**2400**	**36**	**54**
Donor 3 OD	1800	42	50
Donor 3 OS	1800	35	50
Recipient 3	**2200**	**34**	**55**
Donor 4 OD	1800	43	49
Donor 4 OS	1700	36	

*Gasser L, et al. Comparison of corneal endothelial cell measurements by two non-contact specular microscopes. J Ophthalmol. 2015;2015:537942.

Simulation of Fuchs' dystrophy: using a third cornea from which the Descemet's membrane has been removed as the recipient cornea

	ECD (cells/mm²)	CV (%)	HEX (%)
Donor 1 OD	1600	42	42
Donor 1 OS	1800	42	52
Recipient 1	**2300**	**33**	**56**
Donor 2 OD	1700	47	37
Donor 2 OS	1900	44	47
Recipient 2	**2400**	**31**	**53**
Donor 3 OD	1900	46	48
Donor 3 OS	1900	42	45
Recipient 3	**2200**	**34**	**55**
Donor 4 OD	1900	38	48
Donor 4 OS	2000	73	46
Recipient 4	**2800**	**33**	**51**
Gold standard*	> 2000	< 50	> 50

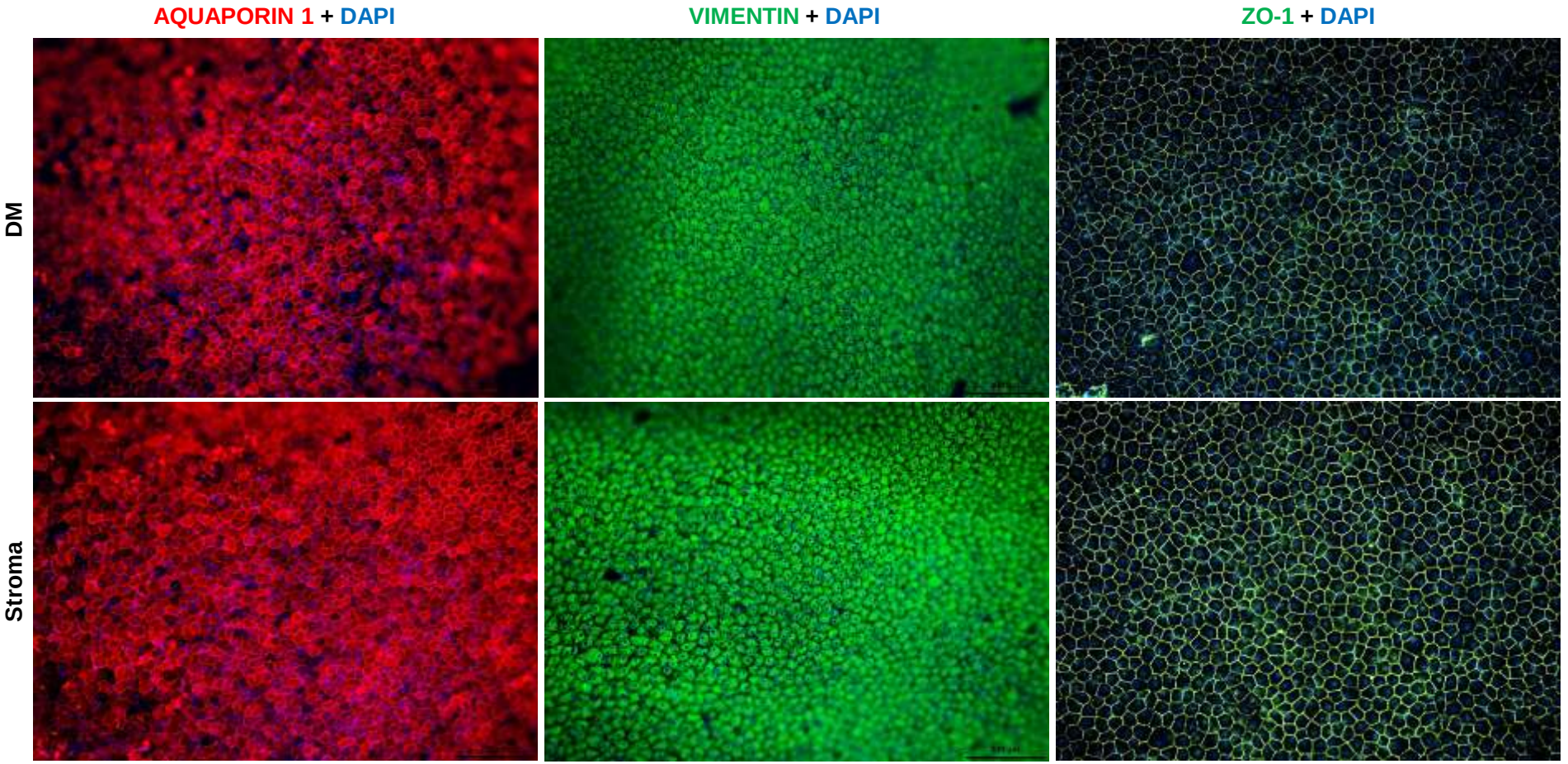
*Gasser L, et al. Comparison of corneal endothelial cell measurements by two non-contact specular microscopes. J Ophthalmol. 2015;2015:537942.

Simulation of Fuchs' dystrophy: using a cornea from the donor as the recipient cornea – in vitro corneal reconstruction simulation

	ECD (cells/mm²)	CV (%)	HEX (%)
Donor 1 OD	1900	42	42
Donor 1 OS	1700	47	42
Recipient 1	**2400**	**33**	**51**
Donor 2 OD	1700	39	47
Donor 2 OS	1800	34	51
Recipient 2	**2300**	**35**	**58**
Donor 3 OD	1500	42	40
Donor 3 OS	1400	42	42
Recipient 3	**2400**	**33**	**51**
Donor 4 OD	1600	41	48
Donor 4 OS	1600	45	44
Recipient 4	**2400**	**41**	**51**
Gold standard*	> 2000	< 50	> 50

*Gasser L, et al. Comparison of corneal endothelial cell measurements by two non-contact specular microscopes. J Ophthalmol. 2015;2015:537942.

Immunofluorescence (magnification 10X)

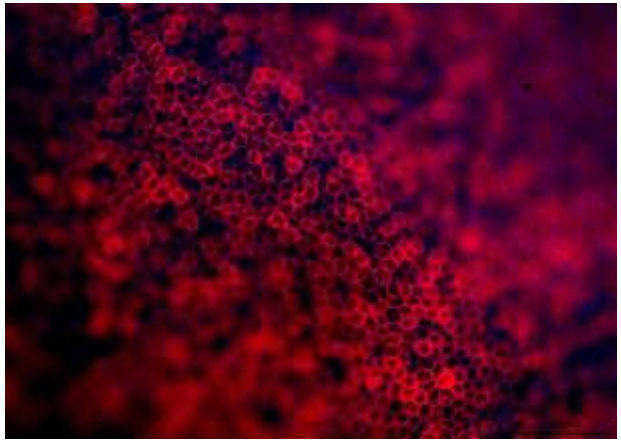


Immunofluorescence (magnification 10X)

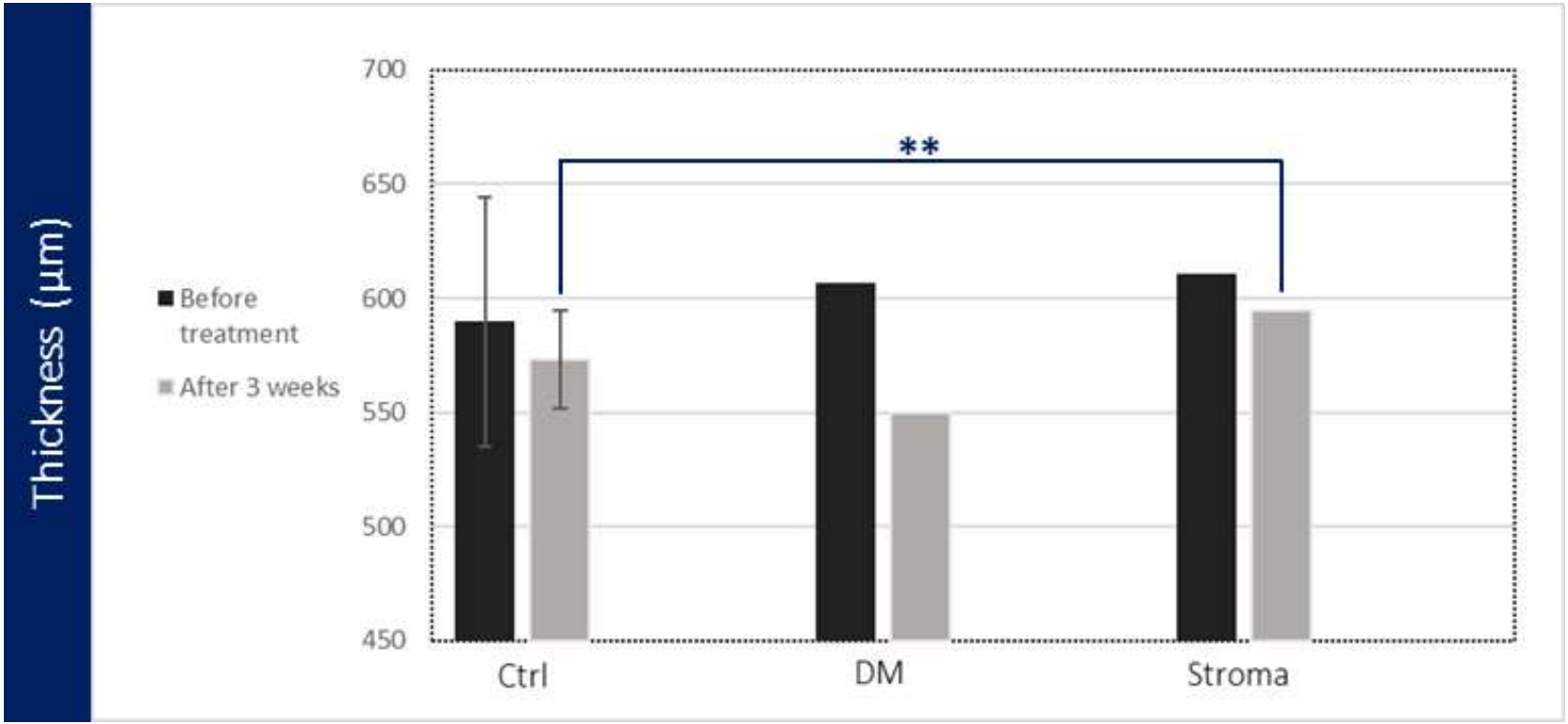
Na^+ / K^+ ATPase + DAPI

DM

Stroma



CENTRAL CORNEAL THICKNESS (in transport - dextran mediu



SNEC will allow to save donor tissues that would be discarded due to low ECD

DISCARDED CORNEAS (in storage)	TOTAL
Medical contraindication	4220
-> Blood/serology test	2353
-> Confirmed/suspected other medical contraindications	1867
Infection	2040
-> Bacterial	858
-> Fungal	505
-> Both	400
-> Unknown	277
Quality	16734
-> Endothelium	13482
-> Stroma	757
-> Other	2495
Outdated	1888
Other (Specify) *	976
TOTAL	25858

*** 2024 EEBA report – over 65.000 donor corneas procured**

cells

MDPI

Article

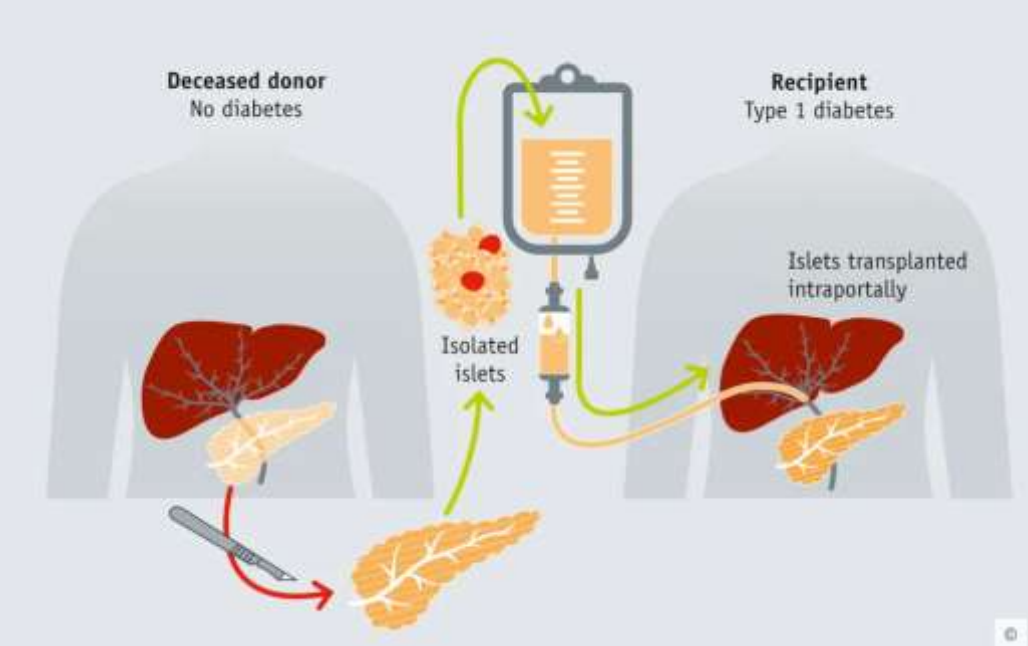
Cell Counting and Cell Cycle Analysis of Simple Non-Cultured Endothelial Cell Injection (SNEC-I) Therapy: Characterization for Clinical Translation

Darren S. J. Ting [1,2,3,4,5,†], Gary S. L. Peh [1,2,†], Dawn J. H. Neo [1], Xiao Yu Ng [1], Belinda Y. L. Tan [1], Raymond C. B. Wong [6], Hon Shing Ong [1,2] and Jodhbir S. Mehta [1,2,7,*]

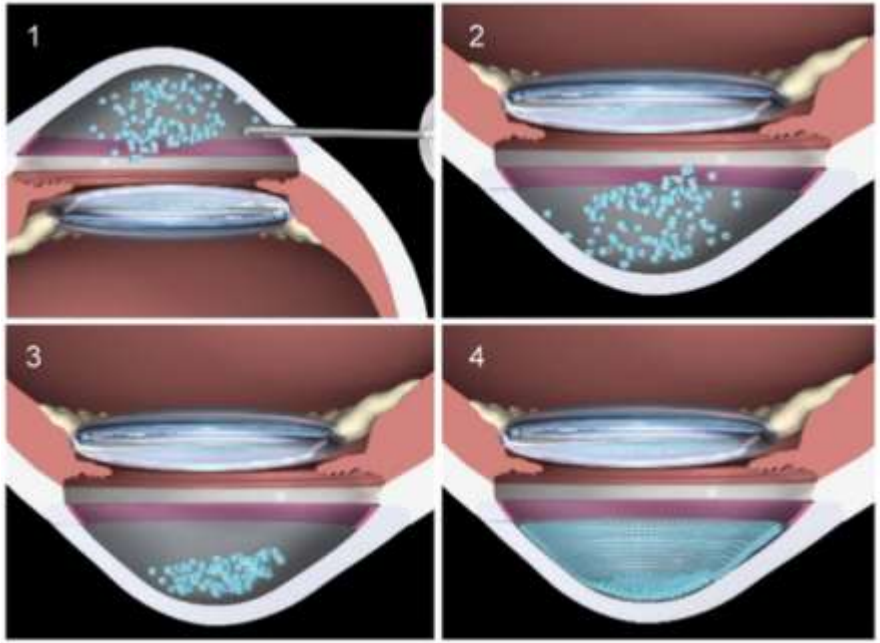
Table 3. Comparison of the cell cycle profiles for various human corneal endothelial cells (CEnCs).

Cell Cycle Status	SNEC-I-Harvested CEnCs	Proliferating CEnCs (M4 + Rock I)	Stabilized CEnCs (M5)	Cell Line B4G12	Cell Line 21T
G1	94.19 ± 3.63	87.25 ± 3.77	92.86 ± 1.56	57.40 ± 10.75 *	71.45 ± 0.64 **
S	0.35 ± 0.23	3.17 ± 1.37 *	0.87 ± 0.77	20.05 ± 8.56 *	10.95 ± 1.48 **
G2/M	0.06 ± 0.07	6.92 ± 2.01 **	3.73 ± 0.83 **	16.40 ± 1.98 **	6.45 ± 0.78 **
Sub-G1	5.20 ± 3.47	2.67 ± 0.61	2.54 ± 0.51	6.15 ± 0.21	11.15 ± 1.63

All values are presented as mean ± standard deviation (SD) %. All experiments were performed with three biological repeats ($n = 3$). Comparison was made between each group, using SNEC-I-harvested CEnC group as the reference group. * $p < 0.05$; ** $p < 0.005$.



- **In Europa:** Le isole pancreatiche sono generalmente considerate **tessuto minimamente manipolato**. Di conseguenza, non rientrano quasi mai nella definizione di medicinale per terapie avanzate (ATMP) o di farmaco, ma sono regolate sotto l'egida dei trapianti di organi e tessuti (Direttiva 2004/23/CE e successiva normativa sulle cellule). La procedura di isolamento è considerata una manipolazione che non cambia le caratteristiche biologiche fondamentali delle isole per la loro funzione d'uso.



CONCLUSIONS

- 6791 donor corneas collected in 2025 in FBOV;
- 30% are not suitable for transplantation;
- 40% of these are not suitable for low ECD (< 2000 cells/mm^2);
- SNEC will allow to use donor corneas that would normally be discarded;
- With SNEC, GMP is NOT needed – **lower costs**;
- *In vivo* injection to obtain ECD > 2000 cells/mm^2
- A new cornea regenerated in vitro with ECD > 2000 cells/mm^2 and ready to be transplanted

RE-DENSE : Reconstituted Endothelial Density via Ex-vivo Non-cultured Seeding

Validation studies from Mehta show that 2 donor corneas with ECD of 1250 cells/mm^2 can lead to 1 cornea with ECD > 2000 cells/mm^2 (Ting DSJ et al., Cells 2025; 14: 986)

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