Excellence Eye Research Centre
Certified as Member of EVICR.net
University "G. d'Annunzio" Chieti-Pescara
Head. Prof. Leonardo Mastropasqua

LENTICULE ADDITION: TESSUTI DEL FUTURO

Mario Nubile
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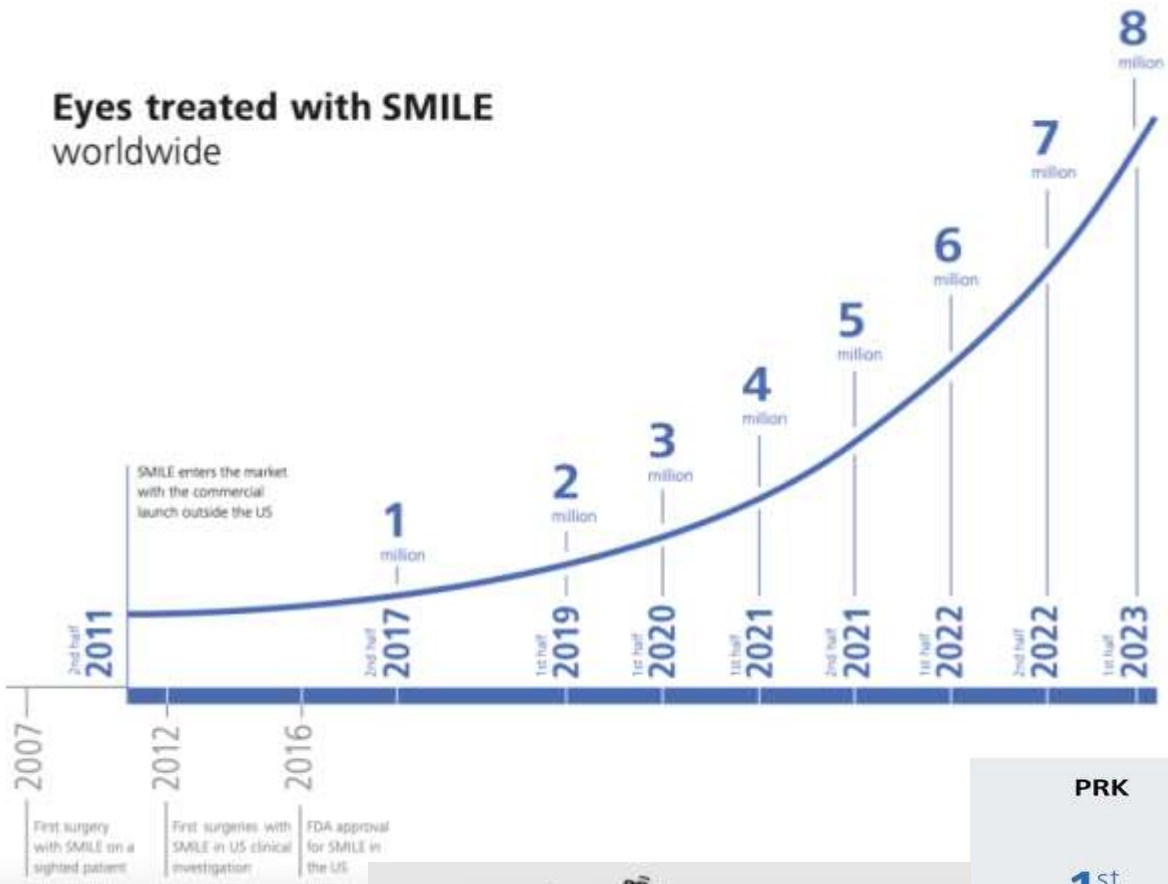
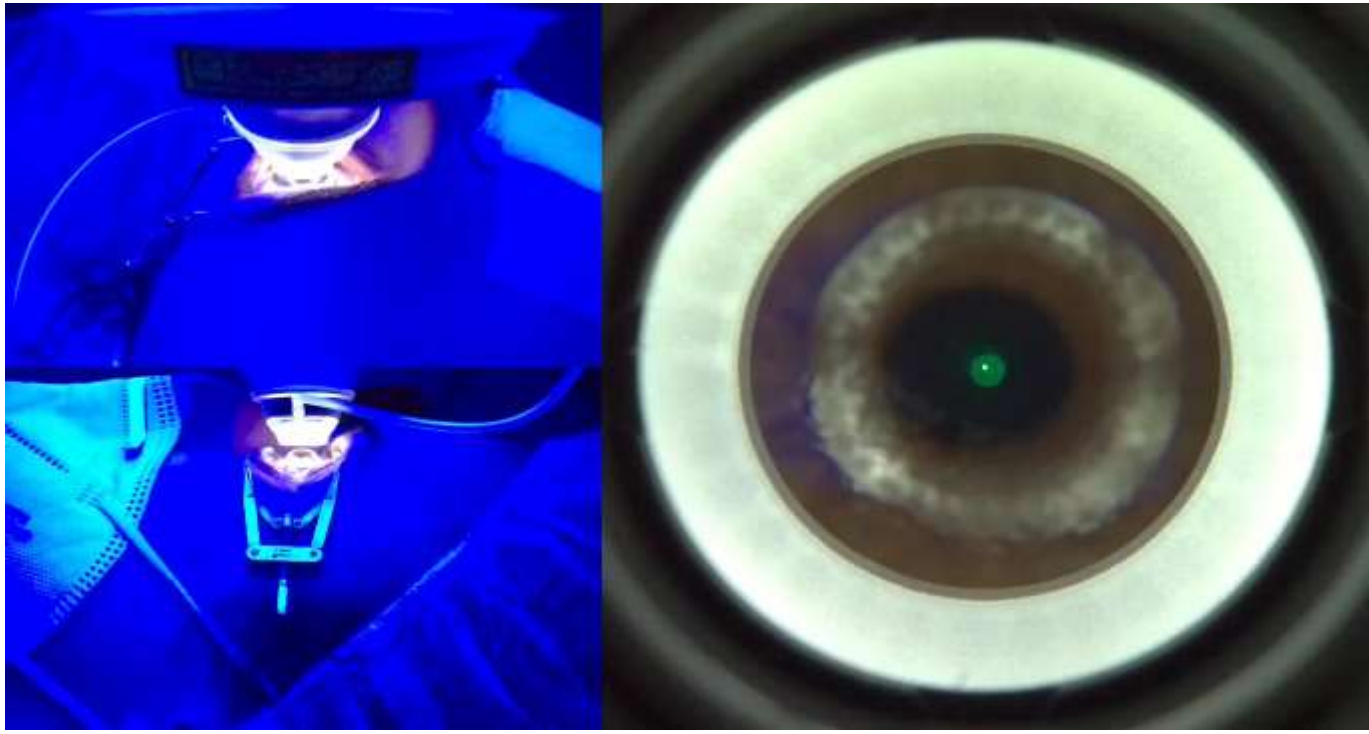
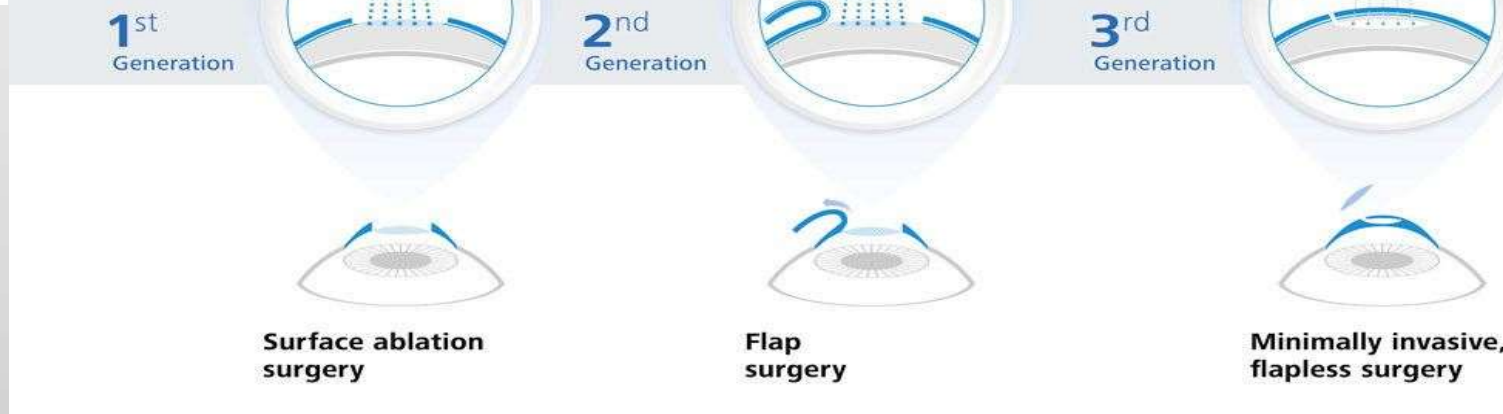
National High-Tech Center (CNAT)
Italian School of Robotic Surgery in Ophthalmology

The premise: Small Incision Lenticule Extraction (SMILE)

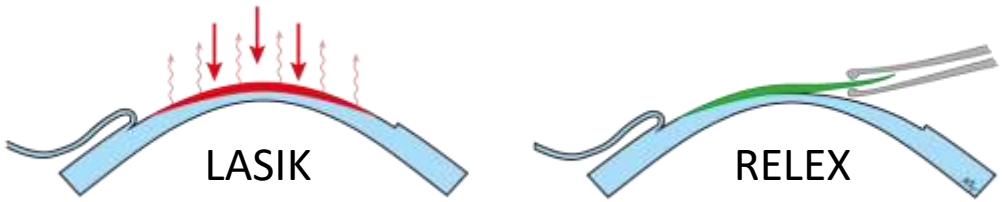






A Reversible procedure

The stromal lenticule extracted following ReLEx **maintain keratocyte viability** and overall **collagen structural integrity** in pre- and post- cryopreserved tissue samples.



Removed tissue is still vital

Extracted lenticule can be reimplanted

«The potential option of stromal lenticule storage after ReLEx offers patients the **unique opportunity of bank their tissue** in case of future need, **or to donate their tissues** to others in need».

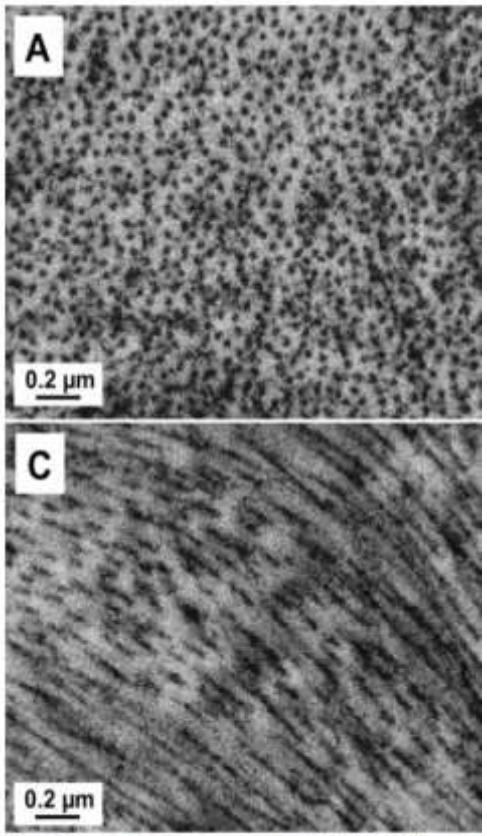
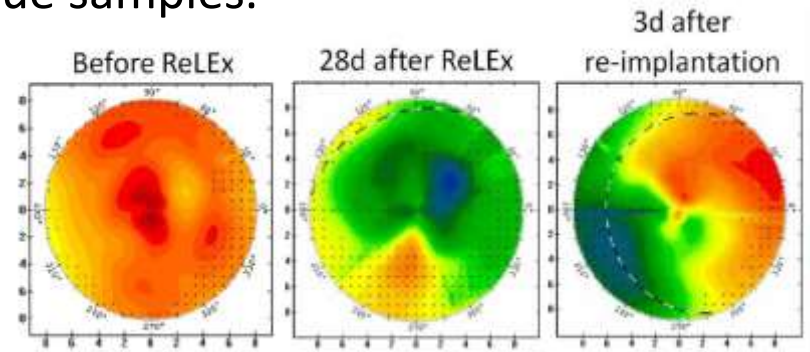
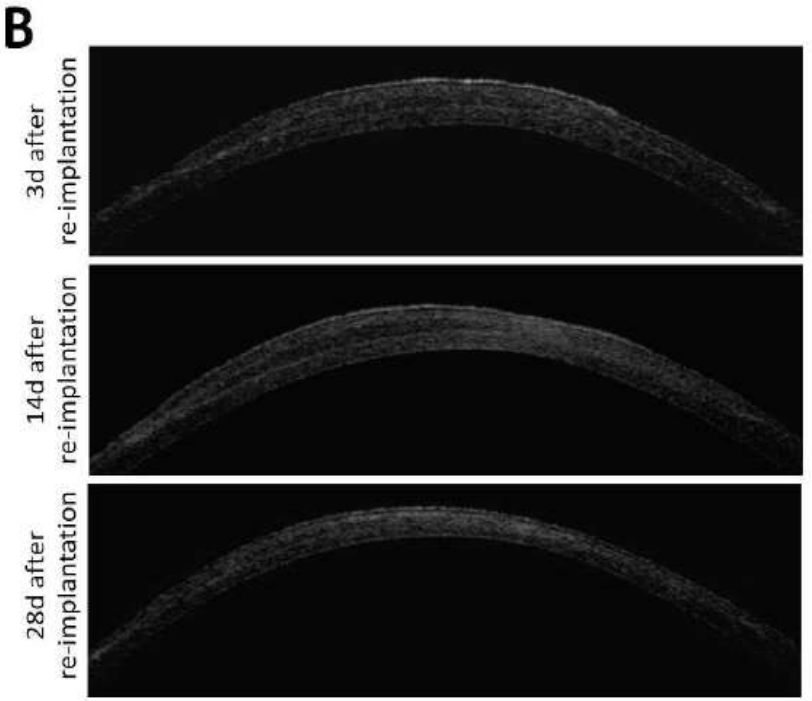


Figure 5. Transmission electron micrographs (TEM) of the stron
Cryopreserved lenticule. A, B: Transversal section of collagen fibrils.





Animal model

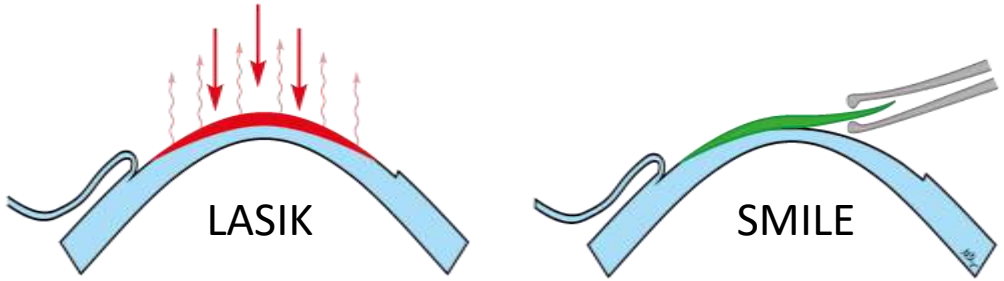
Refractive Lenticule Re-Implantation after Myopic ReLEx: A Feasibility Study of Stromal Restoration after Refractive Surgery in a Rabbit Model

Romesh I. Angunawela,[1,2,5] Andri K. Riau,[1,5] Shyam S. Chaurasia,[1] Donald T. Tan,[1,2,3] and Jodhbir S. Mehta[1,2,3,4]

iovs investigative ophthalmology & visual science

2012

Lenticule banking?



A reversible procedure:

REMOVED TISSUE IS STILL VITAL

The stromal lenticule extracted following ReLEx **maintain keratocyte viability** and overall **collagen structural integrity** in pre- and post- cryopreserved tissue samples.

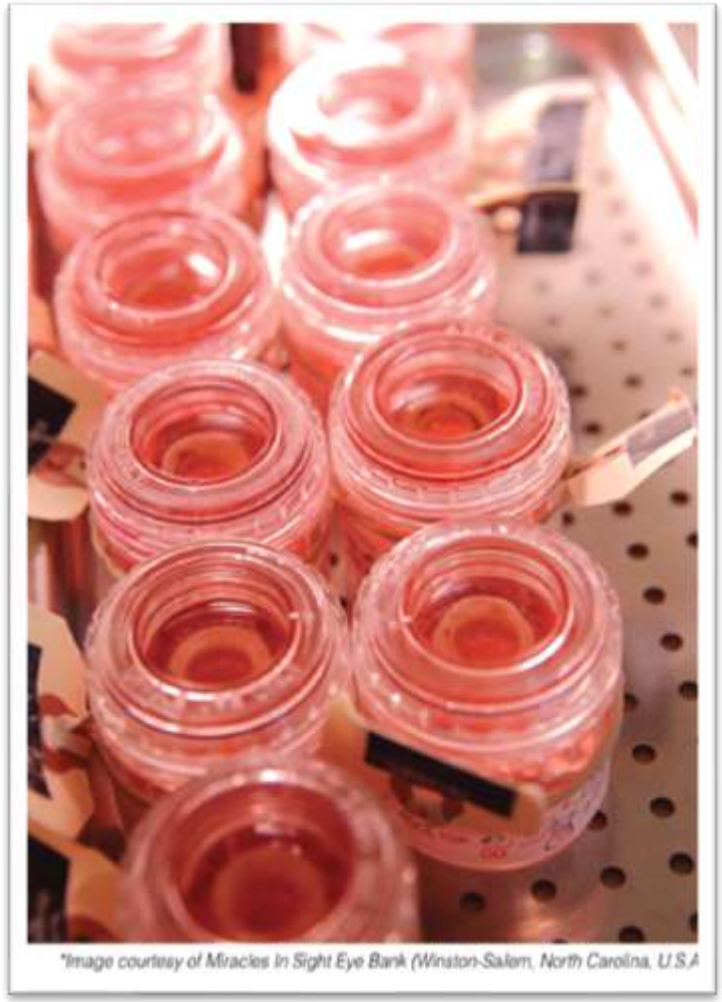


*Image courtesy of Miracles in Sight Eye Bank (Winston-Salem, North Carolina, U.S.A.

«The potential option of **STROMAL LENTICULE STORAGE AFTER RELEX/SMILE** offers patients the unique opportunity of **bank** their tissue in case of future need, **or to donate** their tissues to others in need».

Risk Evaluation of Human Corneal Stromal Lenticules From SMILE for Reuse

Yanfeng Shang, MD, Yu Li, MD, PhD, Zhiqun Wang, MD, Xuguang Sun, MD, PhD, and Fengju Zhang, MD, PhD

Journal of Refractive Surgery 2020

Preservation of corneal stromal lenticule: review

Martina Nemcokova · Jakub Dite · Yun Min Klimesova · Magdalena Netukova · Pavel Studeny

Cell tissue bank - 2021

Experiment-Based Validation of Corneal Lenticule Banking in a Health Authority-Licensed Facility

Andri K. Riau, Kenny P.Y. Boey, Nur Zahirah Binte M. Yusoff, Tze-Wei Goh, Gary H.F. Yam, Kin F. Tang, Catherine S.H. Phua, Hui-Jun Chen, Yoke F. Chiew, Yu-Chi Liu, and Jodhbir S. Mehta

Journal of Tissue Engineering 2022

Banking of corneal stromal lenticules: a risk-analysis assessment with the EuroGTP II interactive tool

Esteve Trias · Paola Gallon · Stefano Ferrari · Ana Rita Piteira · Jaime Tabera · Ricardo P. Casaroli-Marano · Mohit Parekh · Alessandro Ruzza · Antonella Franch · Diego Ponzin

Cell tissue bank - 2020

Stromal lenticules as tectonic patch grafts

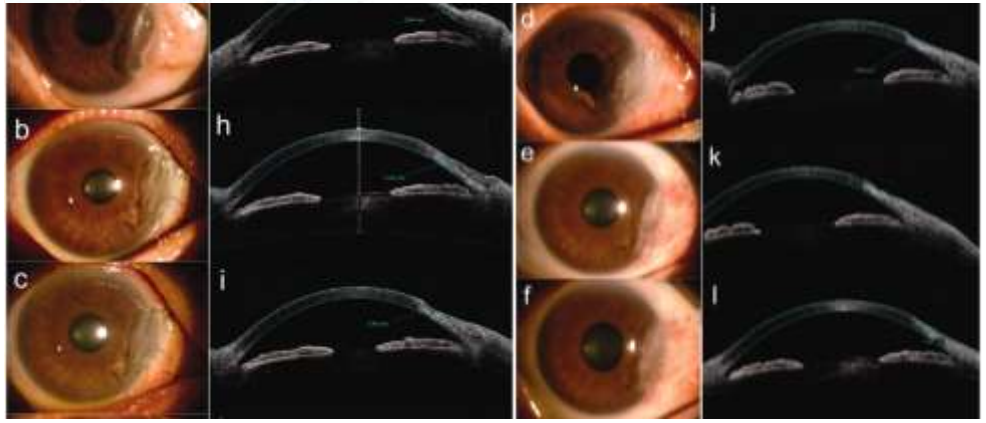
Surgical treatment of corneal dermoid by using intrastromal lenticule obtained from small-incision lenticule extraction

International Ophthalmology 2020
The International Journal of Clinical Ophthalmology and Visual Sciences

Qi Wan [1,2], Jing Tang [3], Yu Han [1], Hongquan Ye [1]

Treatment of Mooren's ulcer coexisting with a pterygium using an intrastromal lenticule obtained from small-incision lenticule extraction: case report and literature review

Na He,[1,#] Wei Song,[2,#] and Ying Gao[1]

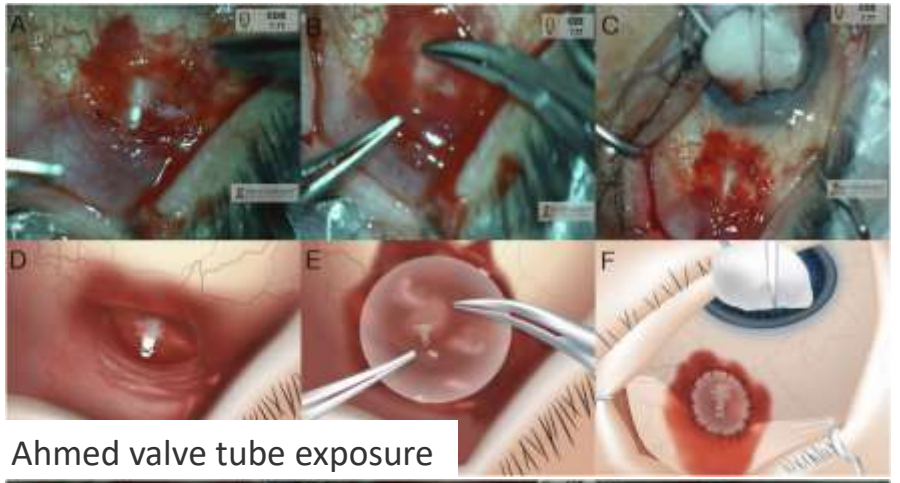


Lenticules from MYOPIC SMILE refractive procedures can be used for Therapeutical purposes

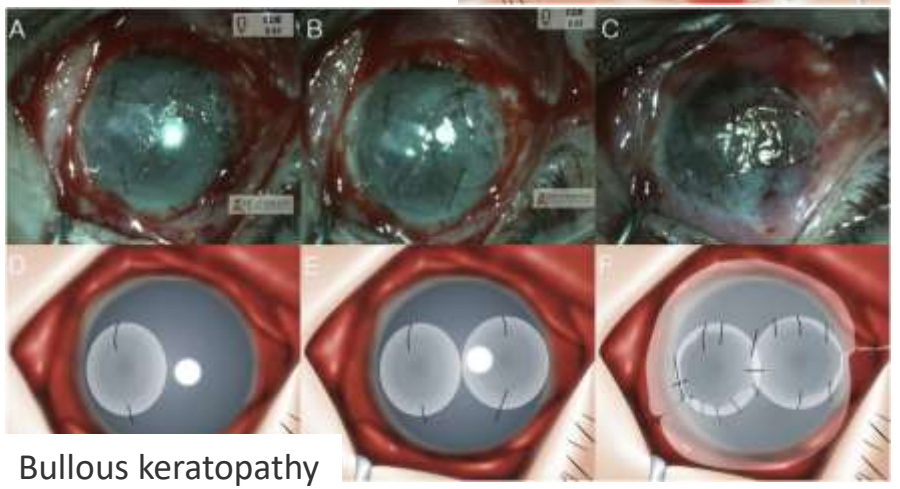
Case series: Use of stromal lenticule as patch graft

Yong Ju Song,[a] Sumi Kim,[b] and Gil Joong Yoon[c,*]

American Journal of Ophthalmology Case Reports 2018

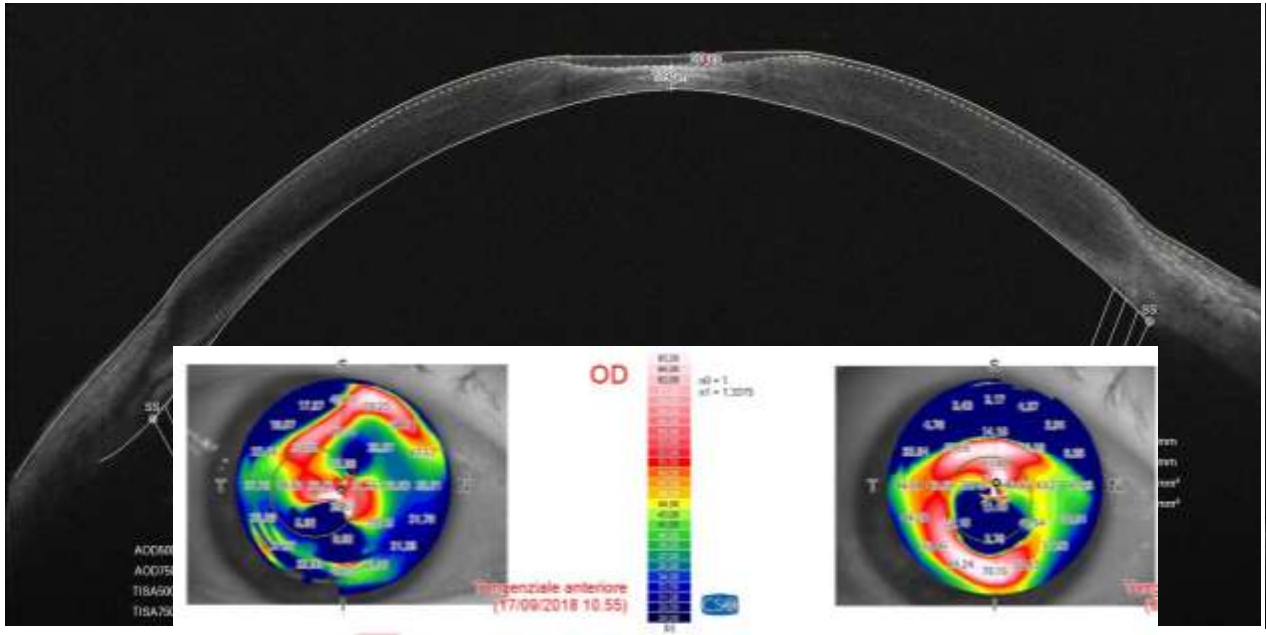


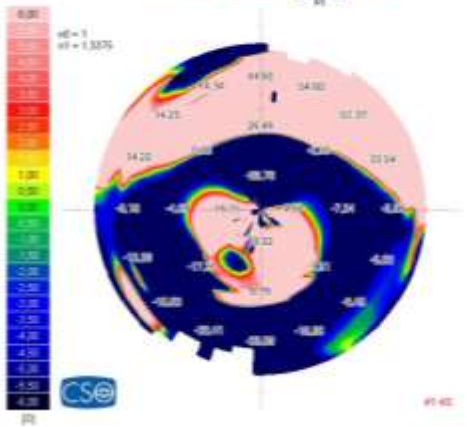
Ahmed valve tube exposure



Bullous keratopathy

Stromal lenticules - addition in corneal diseases





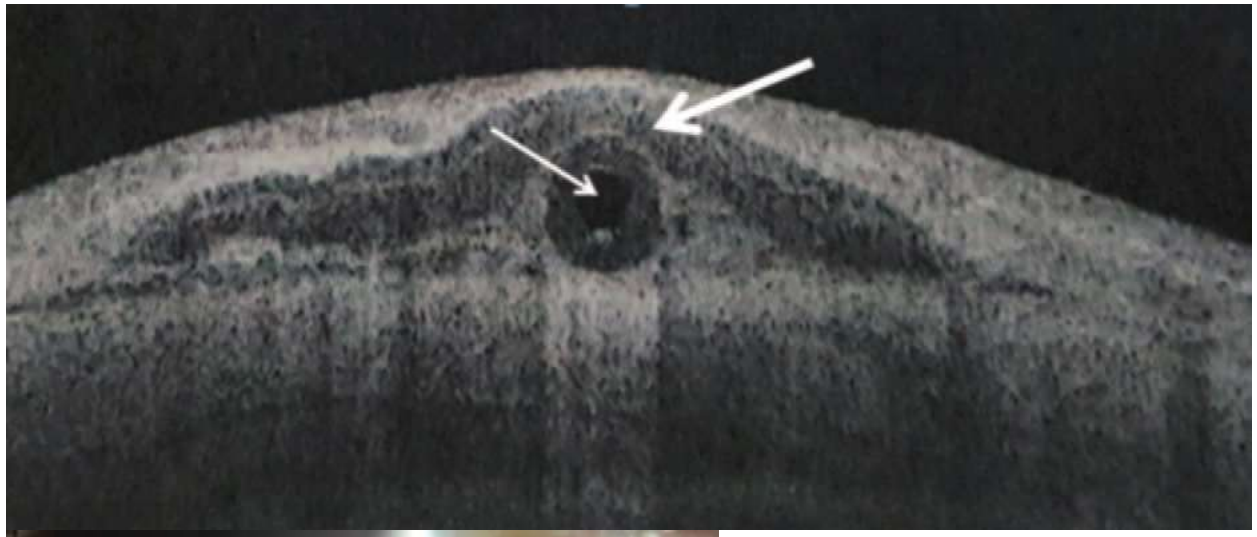
Stromal Lenticule Addition Keratoplasty with MYOPIC SMILE lenticule to re-shape stromal loss in post-HSV stromal scar

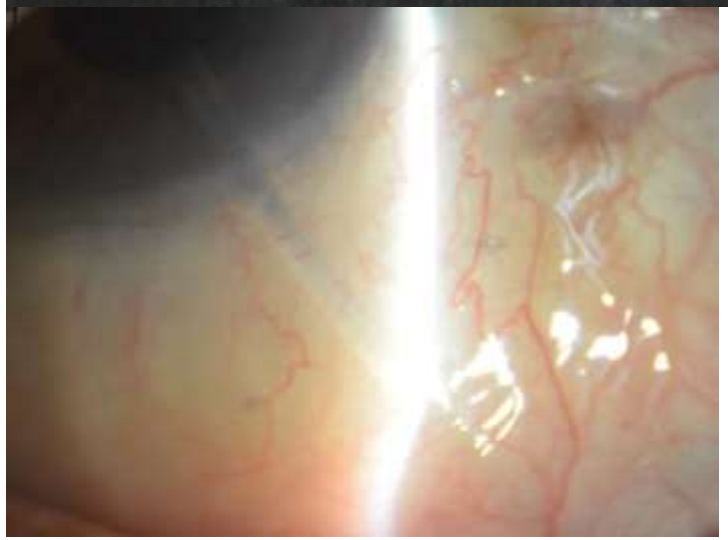
Patch graft in glaucoma drainage implant surgery

Table 1

Advantages and disadvantages of sclera, dura, pericardium and allogeneic cornea.

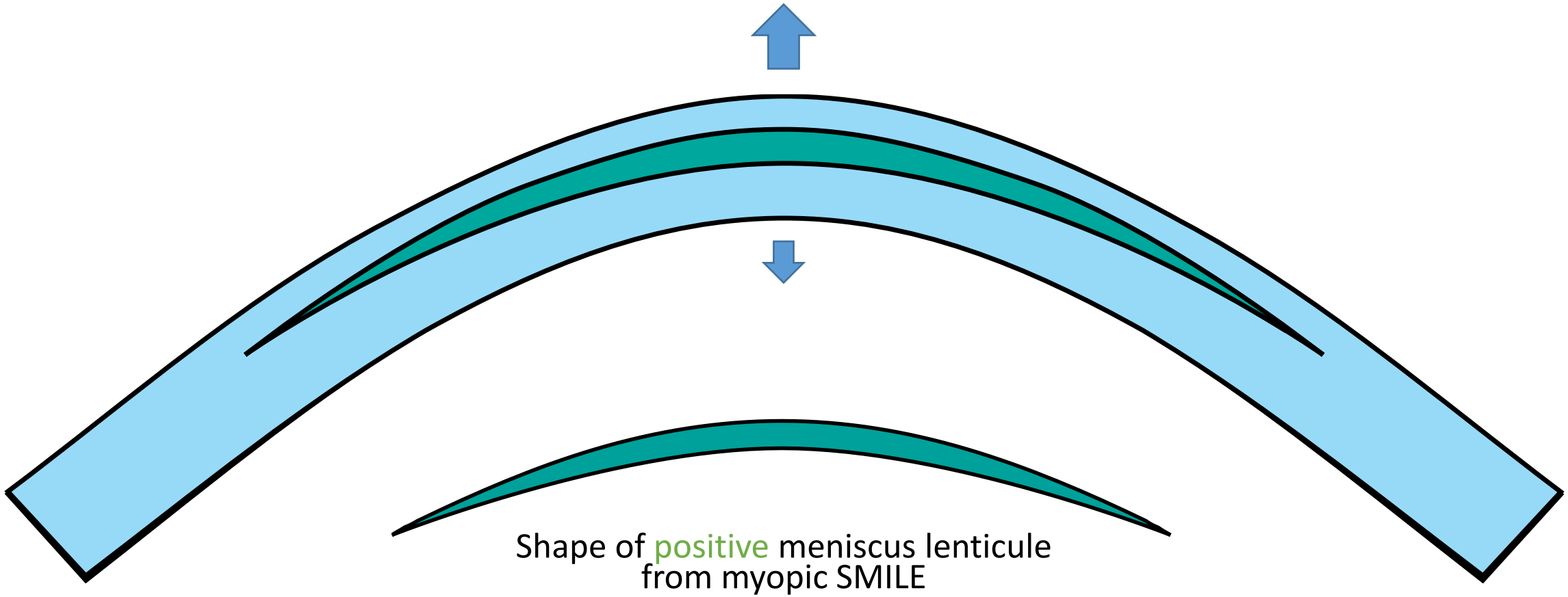
Advantages	Disadvantages
Sclera	
1. Most affordable	1. Can be of variable quality 2. May need thinning (to prevent Dellen) 3. No guarantee of sterility 4. Variably available on an urgent basis secondary to limited shelf life 5. Could be seen through the conjunctiva after surgery
Dura	
1. Longest track record of Use among nonscleral Patch materials 2. Sterile 3. Shelf life ± 5 yr 4. Easily handled	1. Most expensive material
Pericardium	
1. Not as costly as Dura 2. Sterile 3. Shelf life ± 5 years 4. Easily handled	1. Shorter track record of use vs Dura 2. Somewhat variable thickness
Allogeneic cornea	
1. A better cosmetic appearance vs sclera	1. Difficult to obtain 2. Somewhat variable thickness





Wang Y et al. Medicine 2019-2020

Refractive error correction with lenticule implantation



Shape of positive meniscus lenticule
from myopic SMILE

Intrastromal **positive** meniscus
lenticule implantation

→ **Increase** of anterior corneal curvature

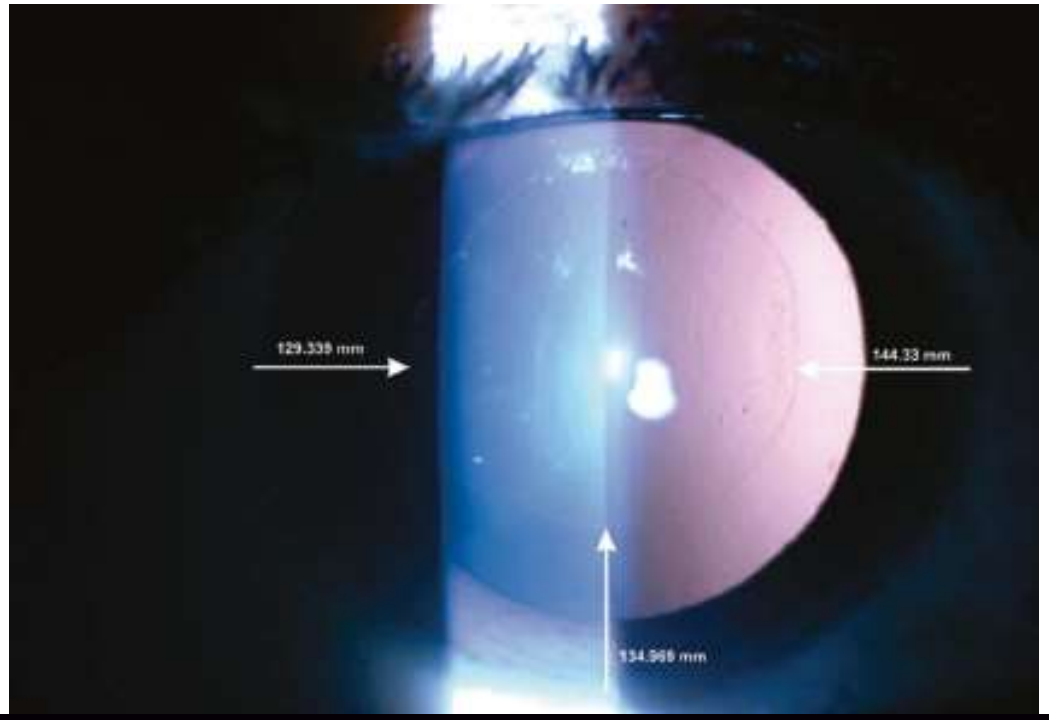
Correction of positive ametropia

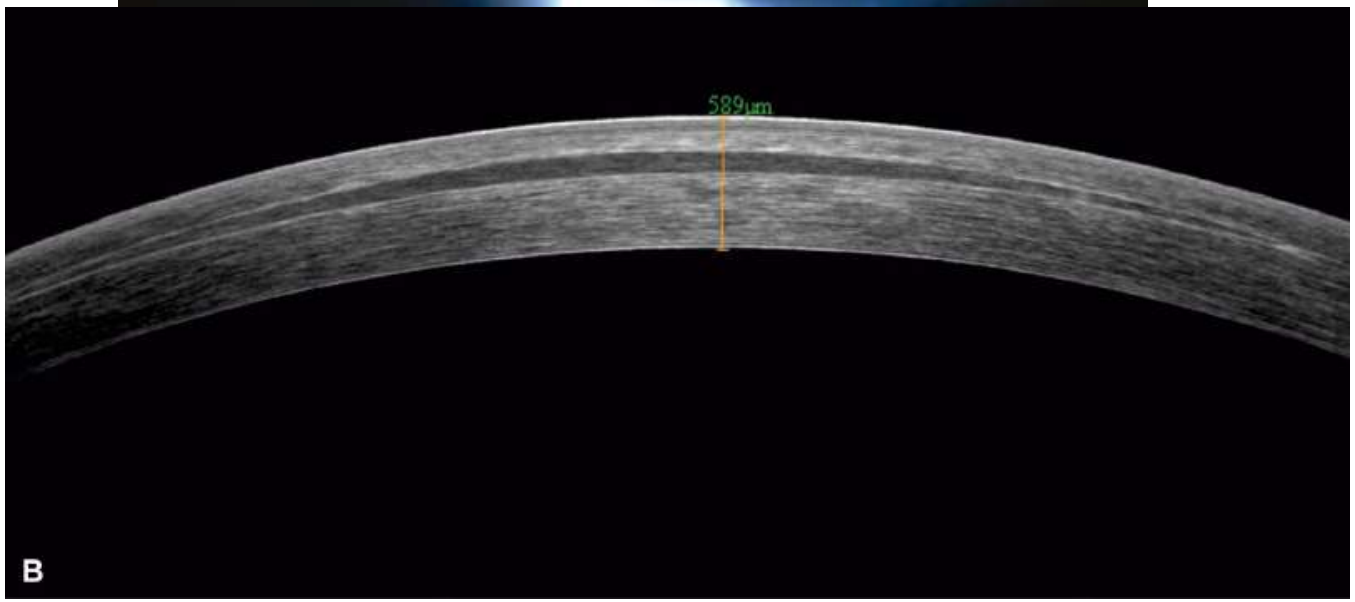
Aphakia (first case)
- Pradhan KR, 2013
- Studer HP, 2015

Hyperopia
- Ganesh S, 2014
- Sun L, 2015
- Liu, 2015
- Damgaard, 2017
- Williams GP, 2018
- Moshirfar, 2018
- Zhang, 2021
- Brar, 2022
- Liu, 2022

Presbyopia
- Presbyiopic monovision -
  - Lim CH, 2013
- PEARL – Jacob, 2017
- Liu, 2018

Astigmatism
- Damgaard, 2019
- Stodulka, 2020





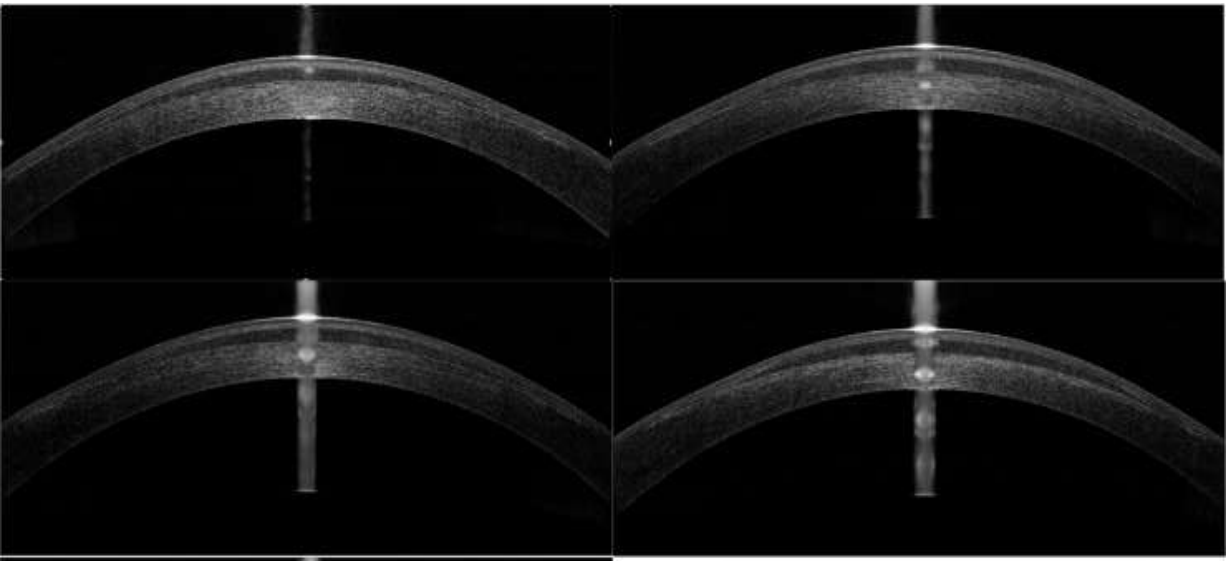
Implantation in human: HYPEROPIA

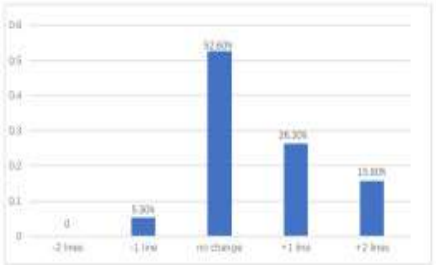
Small incision lenticule extraction (SMILE) combined with allogeneic intrastromal lenticule inlay for hyperopia with astigmatism

Jing Zhang [1 2 3], Yuehua Zhou [1 2 3]

PLOS ONE 2021

The hyperopic eye with astigmatism was first treated with SMILE to correct astigmatism; then a lenticule was extracted from a donor myopic eye and subsequently implanted





Femtosecond Intrastromal Lenticule Implantation (FILI) for Management of Moderate to High Hyperopia: 5-Year Outcomes

Sheetal Brar, MS, Sri Ganesh, MS, DNB, FRCS, Skanda Samak Sriganesh, AS, and Hemali Bhavsar, MS

Journal of Refractive Surgery 2022

«The mean spherical equivalent reduced significantly from +5.50 ± 1.96 to +0.66 ± 1.17 diopters»

Toric Lenticule Implantation for Correction of Hyperopia and Astigmatism Following Small Incision Lenticule Intrastromal Keratoplasty With the Triple Marking Method

Shengtao Liu, MD, PhD, Xiaoxue Zhang, MM, and Xingtao Zhou, MD, PhD

Journal of Refractive Surgery 2022

Comparison of Optical Zone Decentration Following FS-LIKE and SMI-LIKE for Correcting Hyperopia

Shengtao Liu, MD, PhD, Xiaoxue Zhang, MM, Lanhui Yu, MM, Meiyan Li, MD, PhD, and Xingtao Zhou, MD, PhD

2022 Journal of Refractive Surgery

Efficacy and safety of small-incision corneal intrastromal lenticule implantation for hyperopia correction: a systematic review and meta-analysis

Front in Med 2024

Yue Wang[1], Jingjing Zheng[1], Zuofeng Guo[1] and Xuejun Fang[1,2]*

[1]Ophthalmology, Liaoning Aier Eye Hospital, Shenyang, China, [2]AIER School of Ophthalmology, Central South University, Changsha, China

Conclusion: Small-incision intrastromal lenticule implantation may be an effective solution for correcting hyperopia. The effect of improved vision is significant, but further exploration is needed for changes in corneal biomechanics and long-term safety.

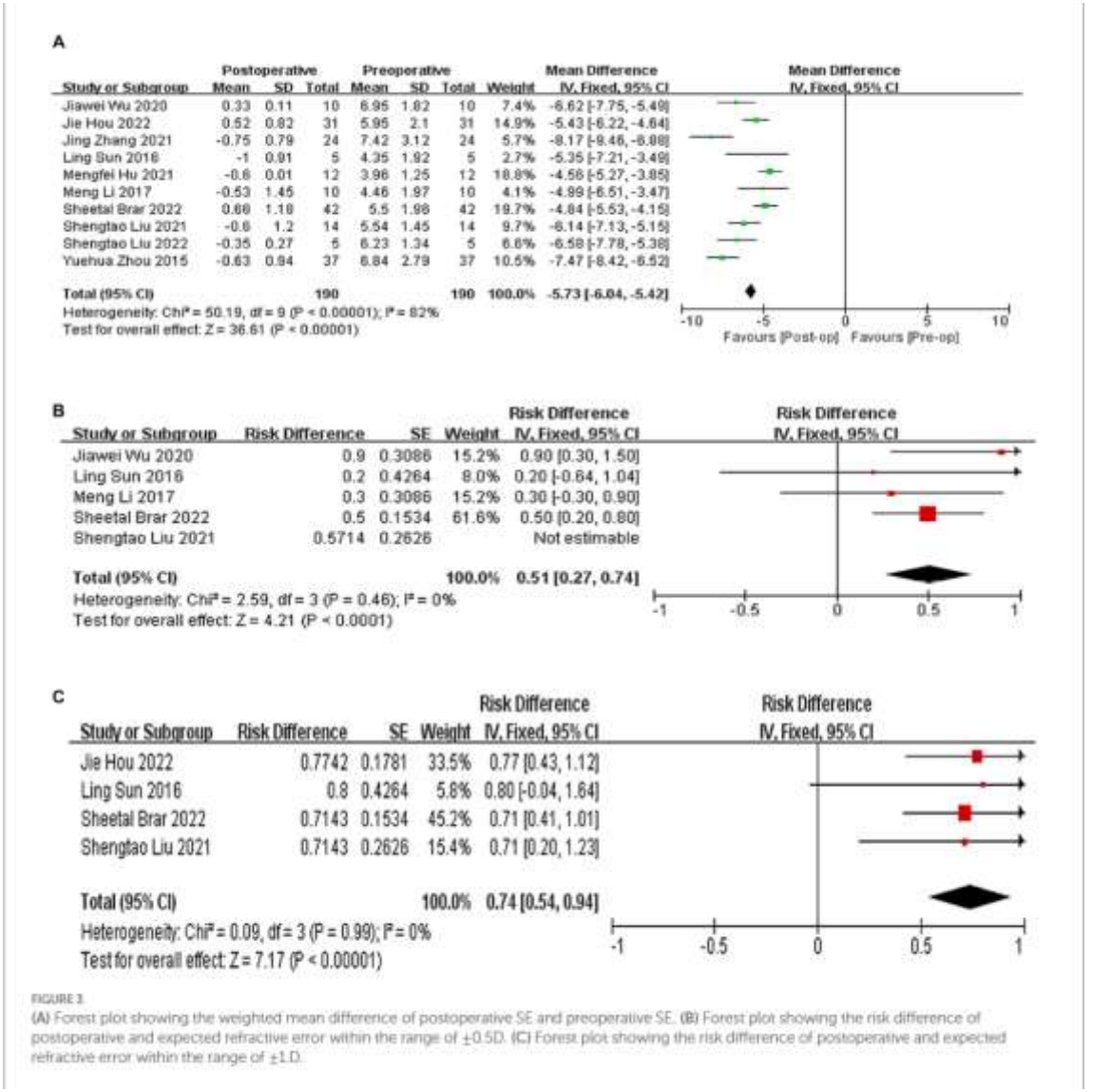


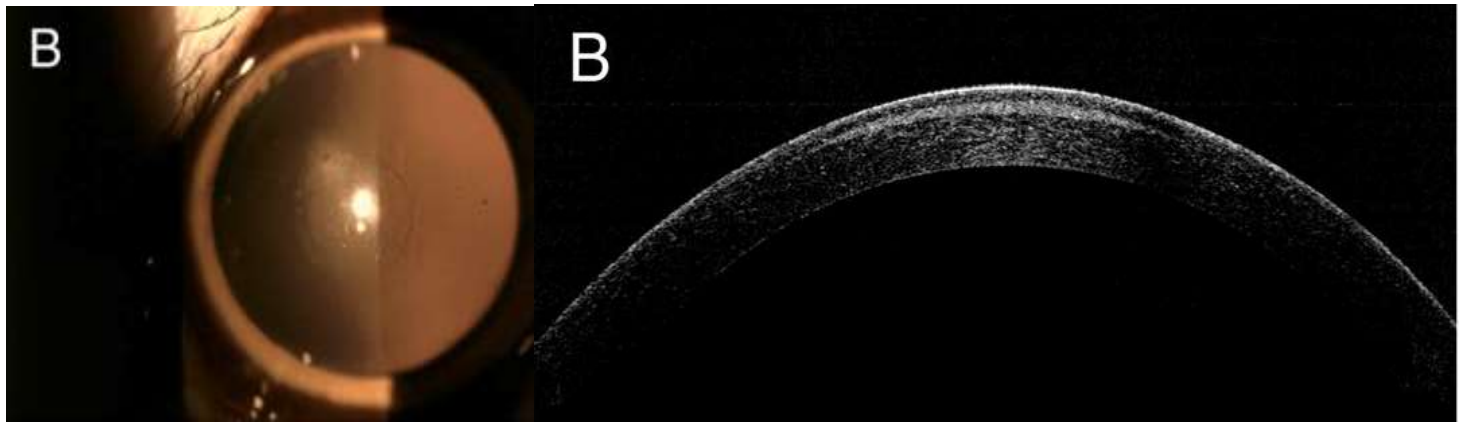
FIGURE 3
(A) Forest plot showing the weighted mean difference of postoperative SE and preoperative SE. (B) Forest plot showing the risk difference of postoperative and expected refractive error within the range of ±0.5D. (C) Forest plot showing the risk difference of postoperative and expected refractive error within the range of ±1.D.

Correction of PRESBYOPIA

Biological corneal inlay for presbyopia derived from small incision lenticule extraction (SMILE)

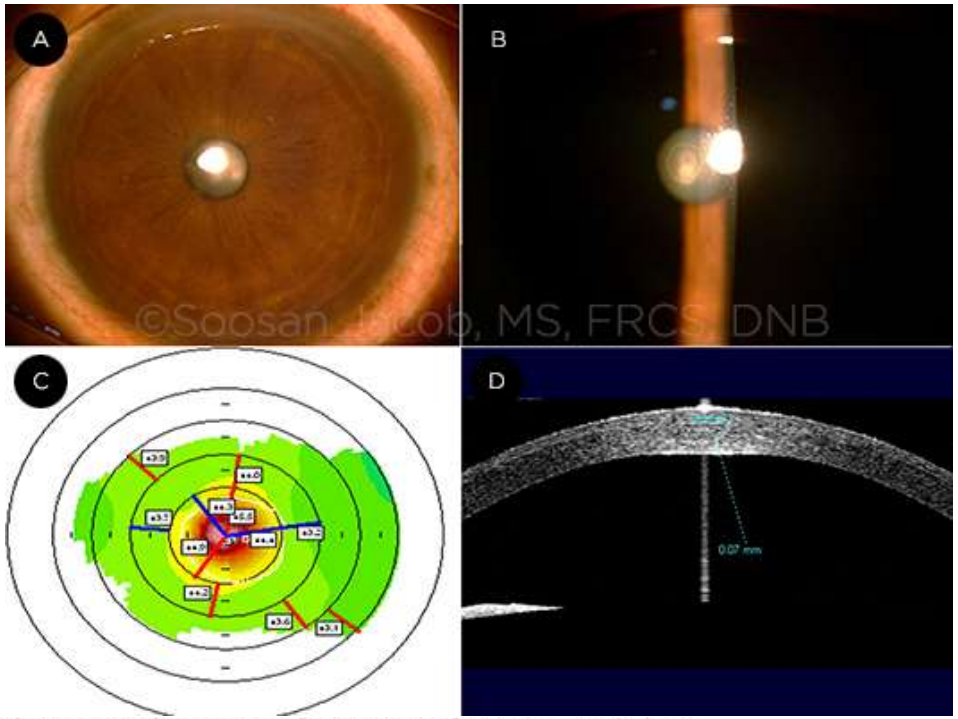
Yu-Chi Liu,[1,2,3] Ericia Pei Wen Teo,[1] Heng Pei Ang,[1] Xin Yi Seah,[1] Nyein Chan Lwin,[1] Gary Hin Fai Yam,[1] and Jodhbir S. Mehta[1,2,3,4]

SCIENTIFIC REPORTS nature research 2018



Convex shaped lenticule (small diameter) hyper-prolate corneal shape, reduced corneal asphericity

Central Corneal **power change** and aberration induction



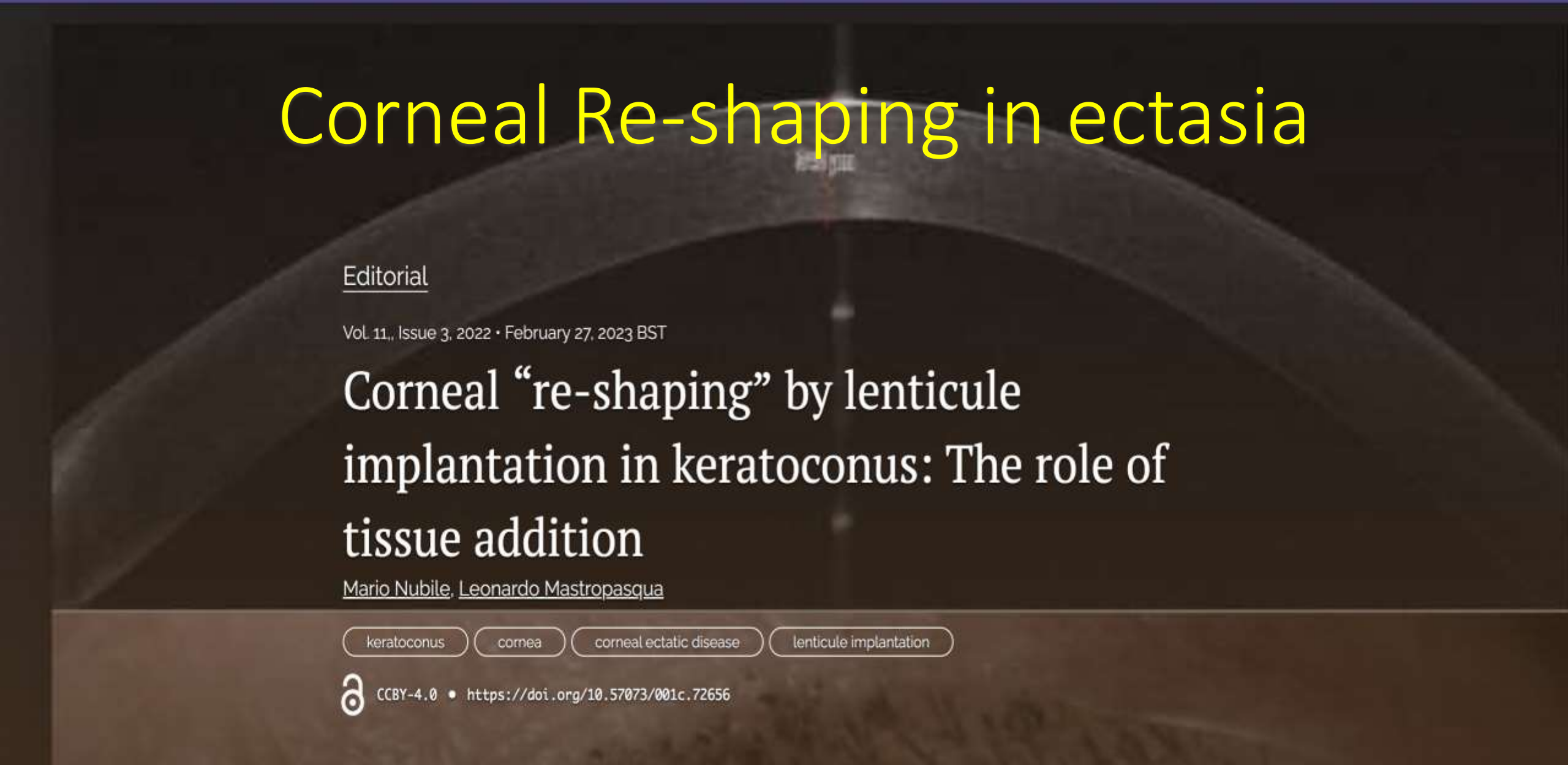
Preliminary Evidence of Successful Near Vision Enhancement With a New Technique: PrEsbyopic Allogenic Refractive Lenticule (PEARL) Corneal Inlay Using a SMILE Lenticule

2017
Journal of Refractive Surgery

Soosan Jacob, Dhivya Ashok Kumar, Amar Agarwal, Athiya Agarwal, Ramalingam Aravind, A I Saijimol

Journal of EuCornea

Corneal Re-shaping in ectasia



Editorial

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Corneal “re-shaping” by lenticule implantation in keratoconus: The role of tissue addition

Mario Nubile, Leonardo Mastropasqua

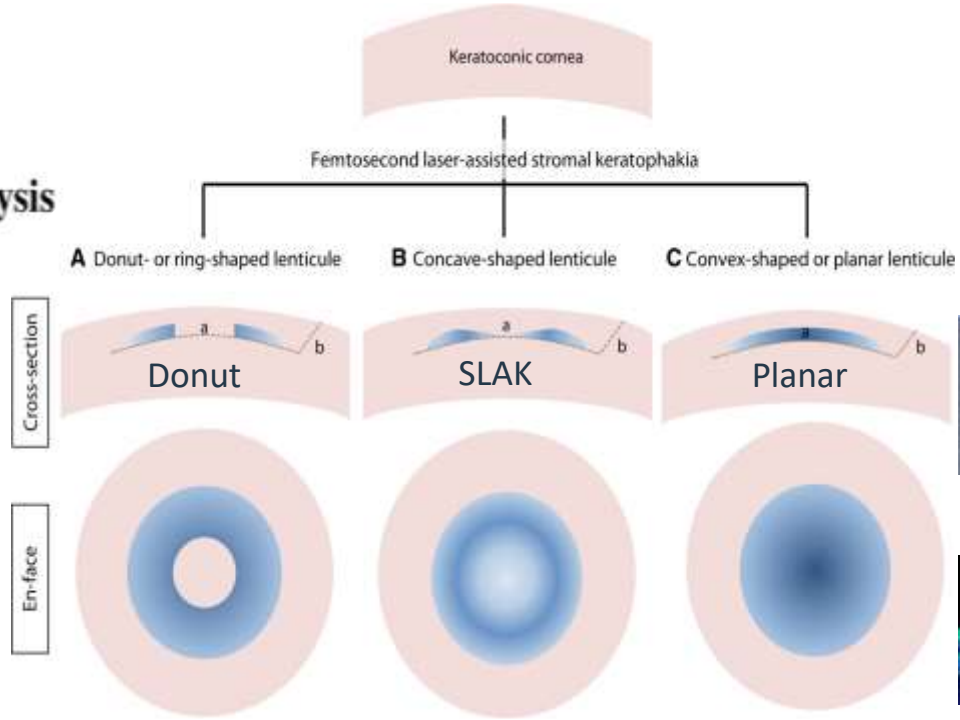
keratoconus cornea corneal ectatic disease lenticule implantation

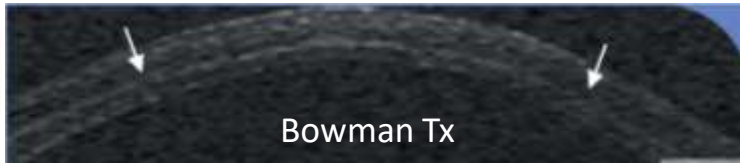
 • https://doi.org/10.57073/001c.72656

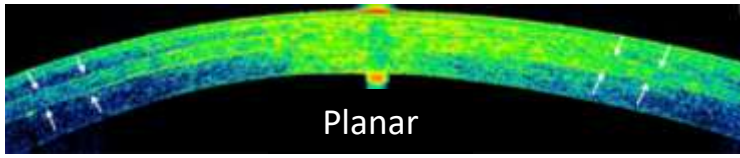
REVIEW 2021

Femtosecond laser-assisted stromal keratophakia for keratoconus: A systemic review and meta-analysis

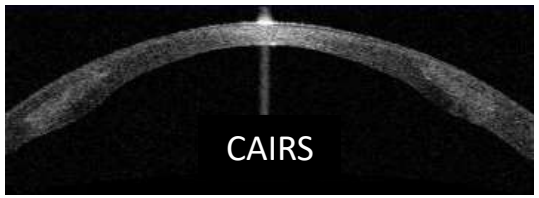
Andri K. Riau · Hla Myint Htoon · Jorge L. Alió del Barrio · Mario Nubile · Mona El Zarif · Leonardo Mastropasqua · Jorge L. Alió · Jodhbir S. Mehta







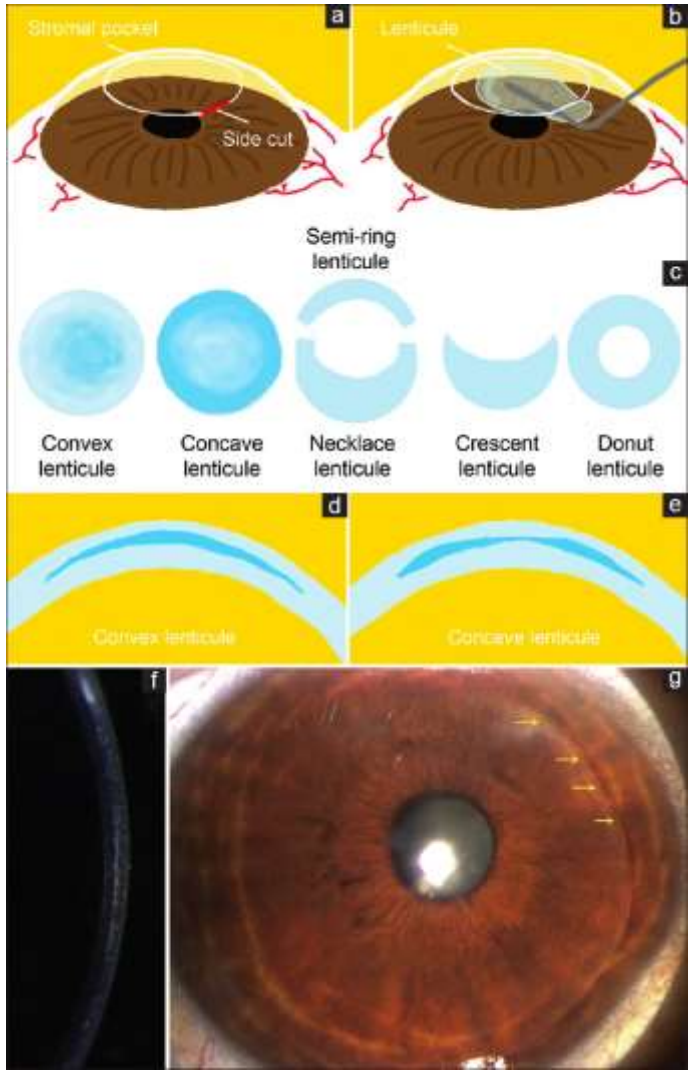
	Km Flattening	SE Change	CCT Increase (µm)	CDVA Lines Gain	Central/ Eccentric cone	Harvest Easiness	Donor Corneas
Planar Lenticules	**+ (-1.8D)**	**+ (+1.7D)**	**117**	**2**	**Both**	**+++**	**1/3**
SLAK	**++ (-5.1D)**	**++ (+3.8D)**	**47**	**1.4**	**Central only**	**++**	**1**
Bowman's Tx	++ (-4.8D)	++ (+3.6D)	21	1	Both	-	1
CAIRS	+ (-2.8D)	++ (+4.1D)	0	2	Both	++	1 (rim)
Donut Lenticule	++ (-3.4D)	+ (+1.7D)	18	3.5	Central only	+++	0 (SMILE lentic)



Lenticule implantation for keratoconus: emerging trend

Studies	Follow-up time	Stage of keratoconus	Clinical outcomes						
			Time	UCVA (LogMAR)	BCVA (LogMAR)	AK1 (D)	AK2 (D)	CCT (μm)	Adverse events
Nubile *et al.*, 2021[8]	6 months	Grades 3–4	Preop.	N.A.	1.07±0.18	Sim-K: 59.63±7.58		408±59	Mild and transient stromal edema
			Postop.	N.A.	0.67±0.22	Sim-K: 57.19±7.32		475±68	
Doroodgar *et al.*, 2020[10]	1 year	N.A.	Preop.	N.A.	0.70±0.17	Mean K 54.68±2.77		383±42	Stromal collagen edema with no inflammation
			Postop.	N.A.	0.49±0.12	Mean K 51.95±2.21		475±41	
Almodin *et al.*, 2018[14]	1 year	Grade 4	Preop.	CF	N.A.	65.90	57.17	245	Mild and transient stromal edema
			Postop.	CF/2 m	N.A.	61.82	60.02	639	
Wei *et al.*, 2022[11]	5 years	Grade 2–3	Preop.	N.A.	1.00±0.19	58.54±2.47	51.60±1.79	434±14	Mild and transient stromal edema
			Postop.	N.A.	0.48±0.13	57.24±2.71	50.11±2.06	610±27	
Semiz *et al.*, 2022[12]	3 years	Grade 2–3	Preop.	1.10±0.17	0.86±0.22	63.53±1.40	56.25±0.94	399±13	Minimal edema, no inflammation or rejection
			Postop.	0.64±0.11	0.47±0.19	57.88±0.96	53.71±0.68	482±8	
Pedrotti *et al.*, 2022[13]	1 year	Grades 3–4	Preop.	N.A.	0.49	57.59±5.69	51.00±6.10	431±68	Perforation of the anterior corneal surface resulting in secondary leucoma
			Postop.	N.A.	0.47	59.29±6.54	52.98±8.83	600±71	
Jadidi *et al.*, 2018[16]	1 year	N.A.	Preop.	0.62±0.39	N.A.	47.58±5.36	43.88±4.17	N.A.	No intraoperational or postoperational complications reported
			Postop.	0.18±0.09	N.A.	46.70±4.18	43.58±1.93	N.A.	
Ganesh *et al.*, 2015[7]	190 days	Grade 1–3	Preop.	1.06±0.48	0.51±0.20	Mean K 53.35±6.90		444±26	No adverse events reported
			Postop.	0.38±0.27	0.20±0.24	Mean K 48.93±8.10		463±27	
Mastropasqua *et al.*, 2018[14]	6 months	Grade 3–4	Preop.	1.58±0.36	1.07±0.17	Mean K 57.98±4.14		N.A.	Transient haze formation
			Postop.	1.22±0.37	0.70±0.23	Mean K 52.83±4.23		N.A.	
Pradhan *et al.*, 2019[17]	1 year	N.A.	Preop.	CF	0.60	64.08	N.A.	N.A.	No complications reported
			Postop.	0.60	0.30	56.74	N.A.	N.A.	
Alió *et al.*, 2019[15]	1 year	Grade 4	Preop.	0.79	0.54	56.83 (47.90–65.40)		456	Limited anterior stromal incision tear during the implantation; scattered haze formation
			Postop.	0.60	0.42	55.25 (46.50–61.80)		536	
Lei *et al.*, 2022[18]	7 months	Grade 4	Preop.	CF/30 cm	N.A.	76.40	74.80	302	Mild and transient stromal edema
			Postop.	0.82	N.A.	68.50	65.20	N.A.	

Preop: Pre-operation; Postop: Post-operation; UCVA: Uncorrected visual acuity; BCVA: Best corrected visual acuity; AK1: Anterior steep keratometry; AK2: Anterior flat keratometry; Sim-K: Simulated keratometry; CCT: Central corneal thickness; PCT: Peripheral corneal thickness; CF: Counting fingers; D: Diopters



Lenticule addition keratoplasty for the treatment of keratoconus: A systematic review and critical considerations

Liu, Yanling et al. IJO 2024

The Rich Promise of Lenticule Transplantation in Keratoconus

A brief history of stromal lenticule addition keratoplasty.

BY LEONARDO MASTROPASQUA, MD; AND MARIO NUBILE, MD

CRST 2019

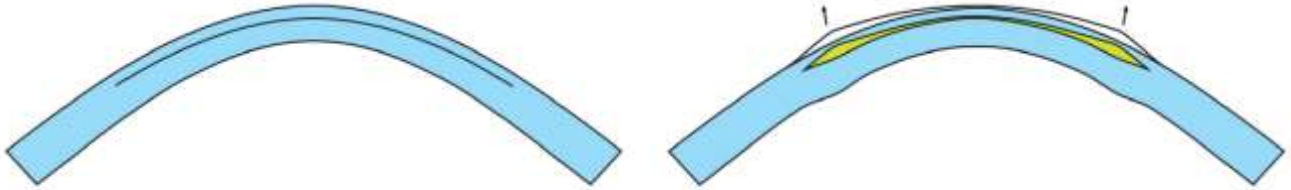


Figure 1. Drawing depicting the SLAK procedure: The negative meniscus-shaped lenticule is implanted intrastromally to improve the geometrical quality of keratoconic corneas.

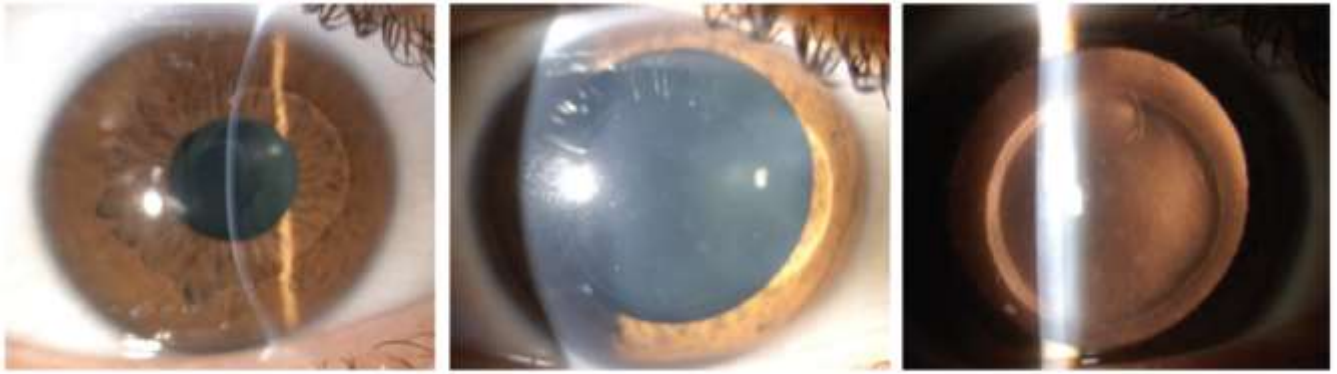
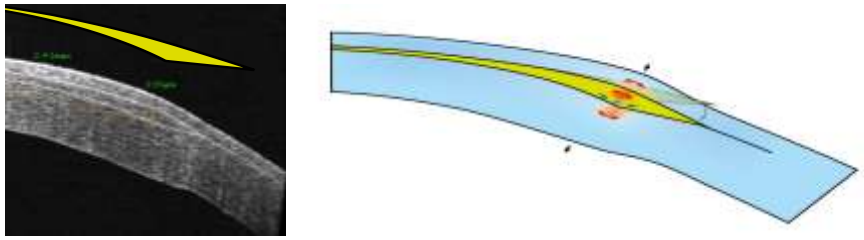


Figure 2. SLAK in advanced keratoconus: The stromal interface transparency was stable over 18 months of follow-up (left to right).

Conclusion The implantation of modified hyperopic-shaped intra-corneal stromal lentoid is a feasible and reproducible technique for achieving central corneal flattening while increasing thickness. Whether

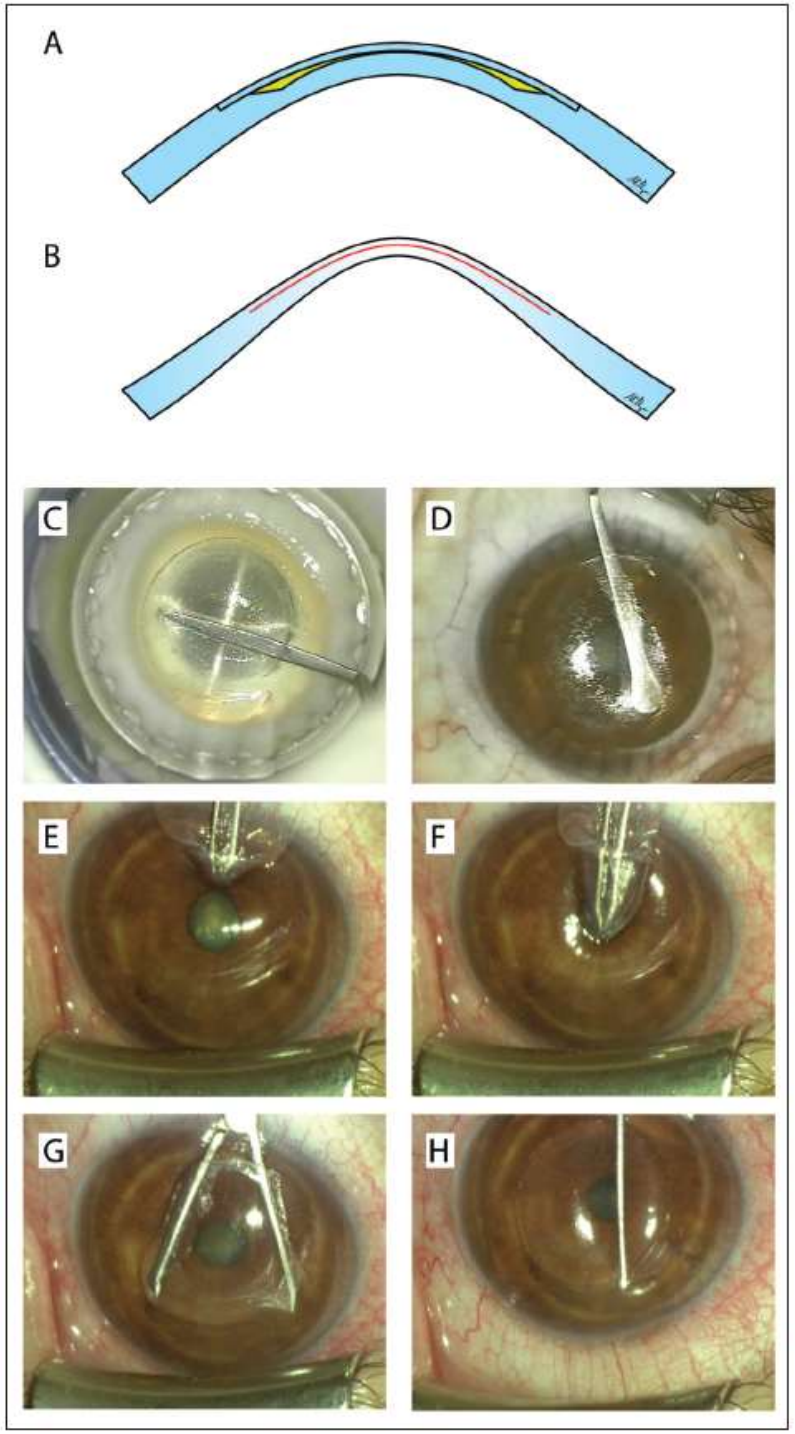
Mastropasqua L, Nubile M.
Int Ophthalmol 2016



WHAT IS SLAK?

Stromal Lenticule Addition Keratoplasty entails implanting a negative meniscus-shaped lenticule that is thinner in the center and thicker in the periphery—the geometric opposite of a myopic lenticule—to reshape and stabilize the corneas in eyes with progressive keratoconus.

The basic idea of SLAK surgery is to implant the lenticules intrastromally in order to improve the geometrical quality of pathological corneas affected by keratoconus.

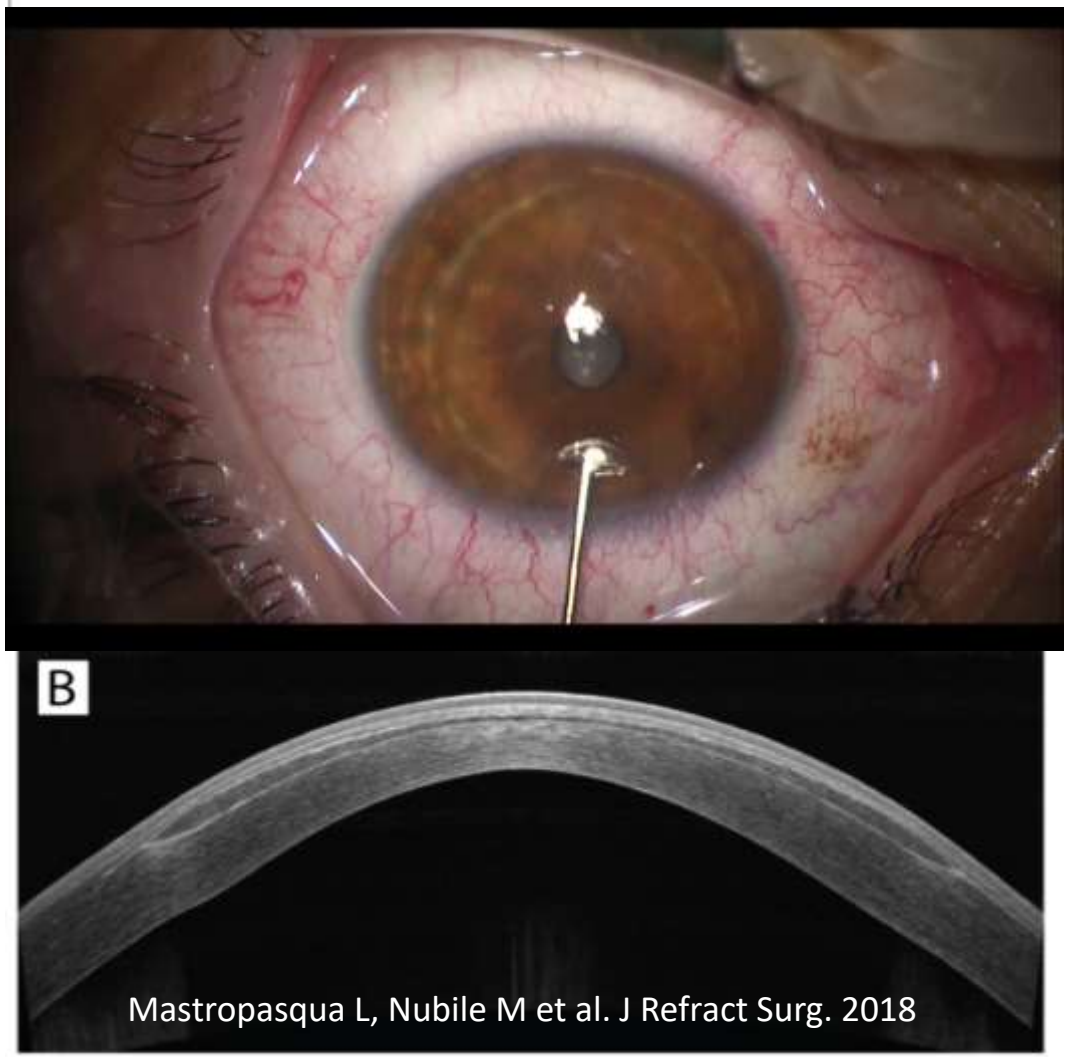


SLAK

THERAPEUTIC REFRACTIVE SURGERY

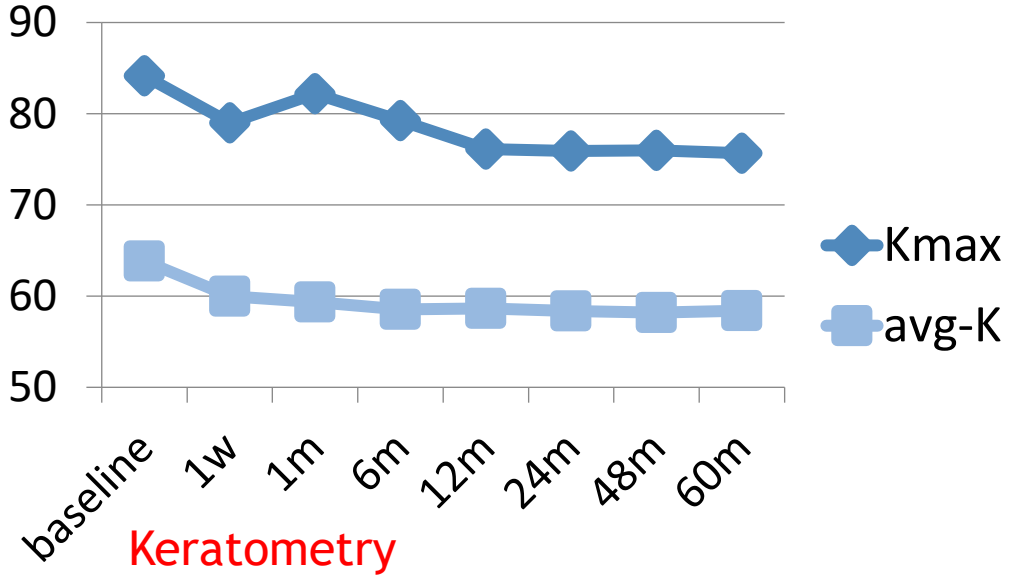
Femtosecond Laser–Assisted Stromal Lenticule Addition Keratoplasty for the Treatment of Advanced Keratoconus: A Preliminary Study

Leonardo Mastropasqua, MD; Mario Nubile, MD, PhD; Niccolò Salgari, MD; Rodolfo Mastropasqua, MD

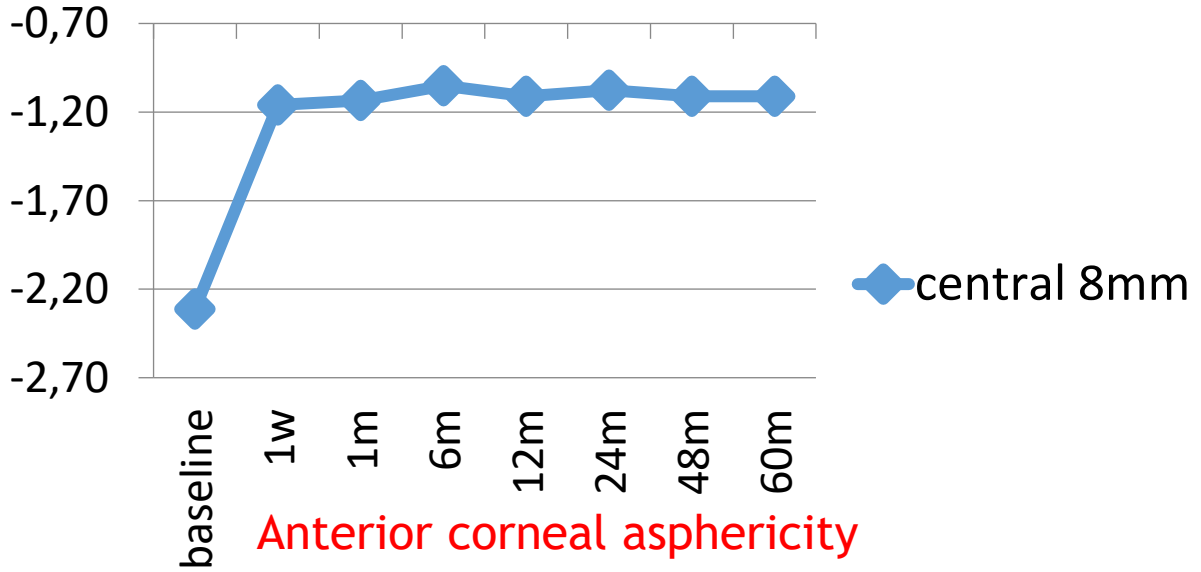


Mastropasqua L, Nubile M et al. J Refract Surg. 2018

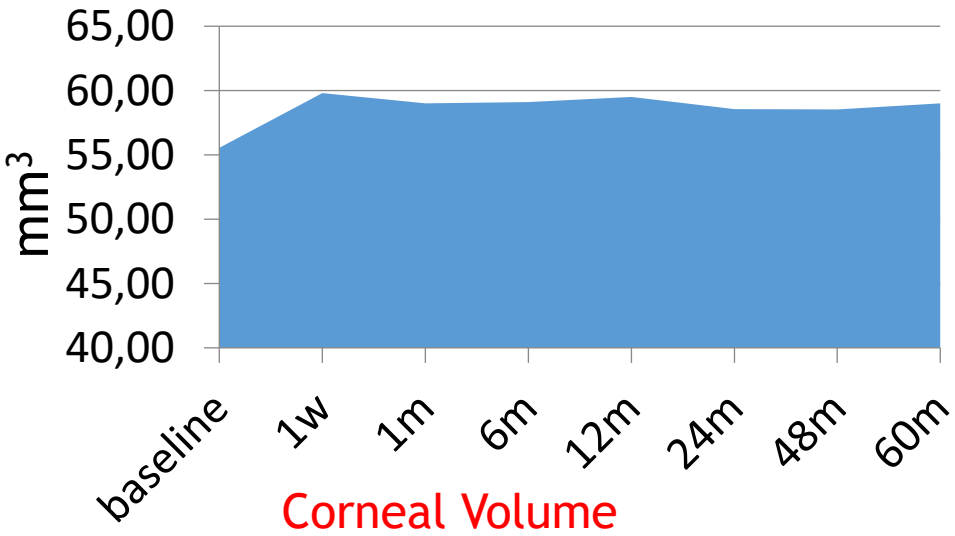
Extended follow-up results (60 months)



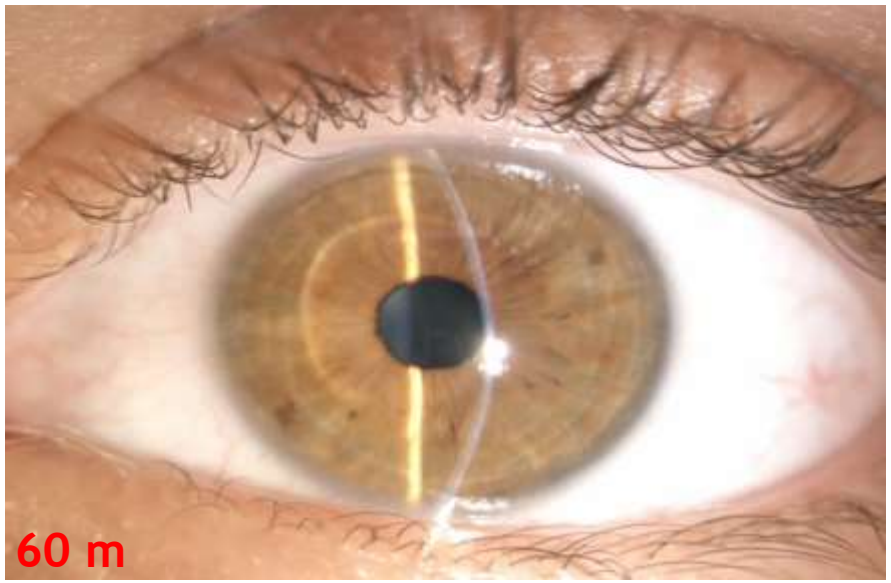
Keratometry



Anterior corneal asphericity



Corneal Volume



ORIGINAL ARTICLE [J Refract Surg. 2020;36(8):544-550.]

In Vivo Confocal Microscopy of Stromal Lenticule Addition Keratoplasty for Advanced Keratoconus

Leonardo Mastropasqua, MD; Niccolò Salgari, MD; Erminia D'Ugo, MD; Manuela Lanzini, MD; Jorge L. Alió del Barrio, MD, PhD; Jorge L. Alió, MD, PhD; Beatrice Cochener, MD; Mario Nubile, MD, PhD

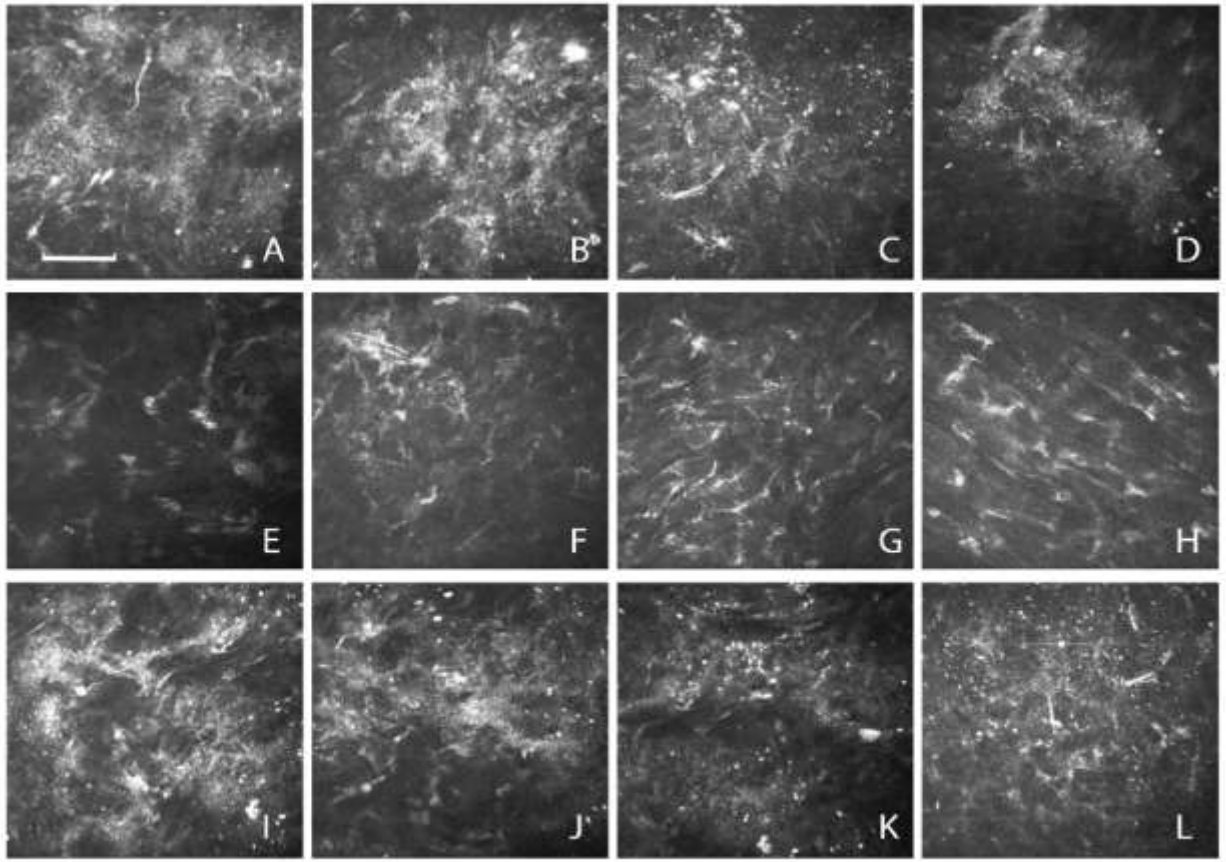


Figure A. Anterior and posterior lenticule interfaces appeared hyperreflective at 1 week (A and I, respectively) with presence of cellular and matrix debris. Reflectivity gradually decreased over time (B and J at 1 month; C and K at 3 months) but was still noticeable at 12 months (D and L). (E) Edema with reduced keratocyte density in lenticule stroma was observed at 1 week. (F) At 1 month, edema subsided but keratocyte nuclei still appeared reduced in number and altered in morphology. Cell density gradually increased and morphology improved over time (G: 3 months) but nuclear shape still appeared irregular at 12 months (H). (Caliper is 100 µm.)

TABLE 1
Mean Subbasal Nerve Density (mm/mm²), Mean Keratocyte Density (cell/mm²), and Relative Donor-Recipient Interface Reflectivity

		Keratocyte Density		Relative Reflectivity	
Time	Subbasal Nerve Density	Anterior Stroma	Posterior Stroma	Anterior Interface	Posterior Interface
Preoperative	13 ± 3	760 ± 115	583 ± 85	–	–
1 week	4 ± 2	663 ± 98	450 ± 90	46.3 ± 18.1	48.6 ± 20.1
1 month	3 ± 2	699 ± 86	485 ± 97	42.4 ± 15.0	42.1 ± 18.2
3 months	11 ± 2	730 ± 93	505 ± 87	25.6 ± 16.1	28.8 ± 13.0
6 months	12 ± 5	724 ± 107	531 ± 71	25.3 ± 14.3	29.0 ± 15.1
12 months	12 ± 2	748 ± 103	567 ± 73	24.8 ± 10.2	23.9 ± 14.0

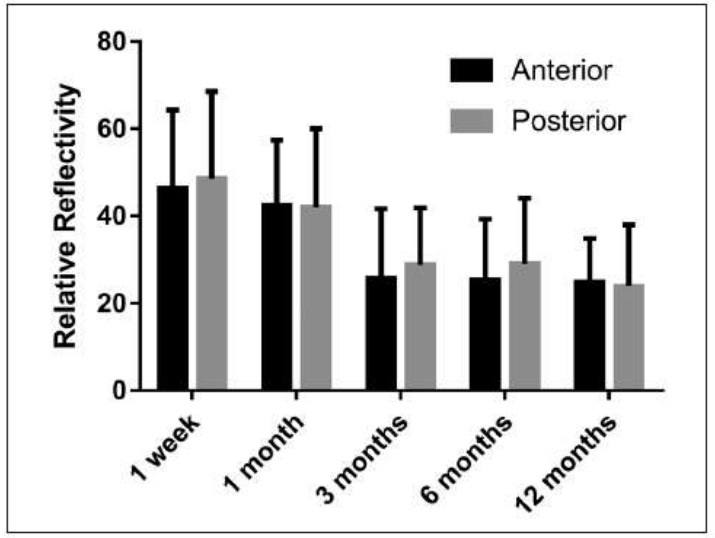


Figure 2. Relative reflectivity level of the anterior and posterior stromal interfaces between donor and recipient.

SLAK:

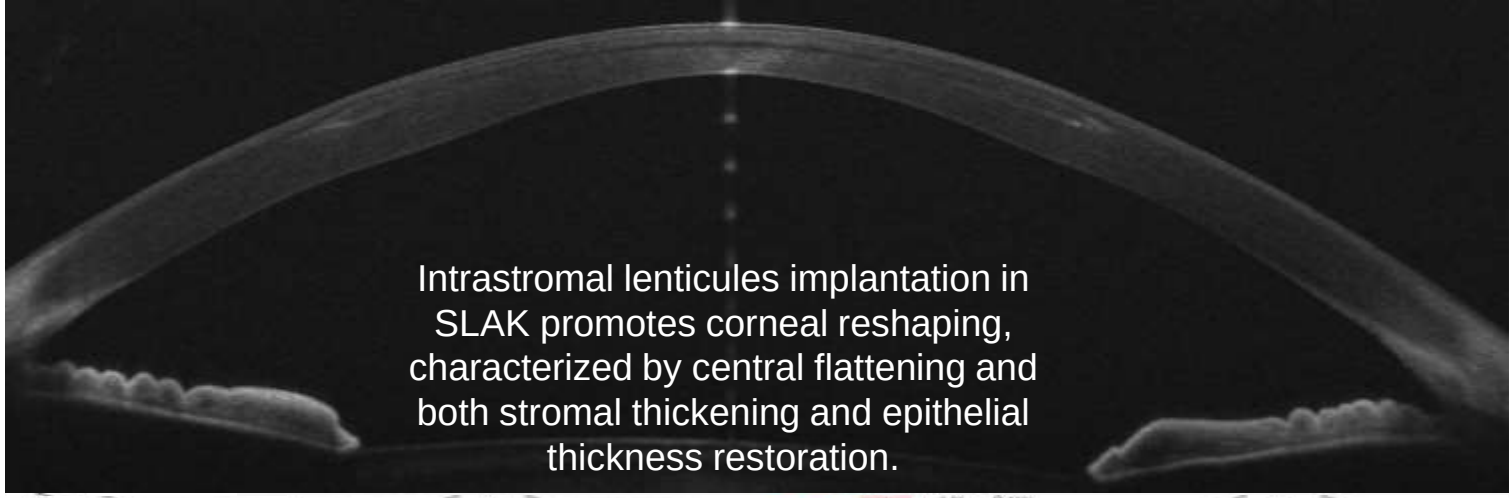
Mild wound healing reaction,
stable interface reflectivity, absence of immune stromal rejection

CONCLUSIONS: Stromal lenticule addition keratoplasty produces transitory nerve plexus density reduction and minor inflammatory reaction that rapidly decreases during the first month. Donor-recipient interface reflectivity is comparable to a femtosecond laser refractive procedure with no sign of stromal opacification or stromal rejection in 1 year of follow-up.

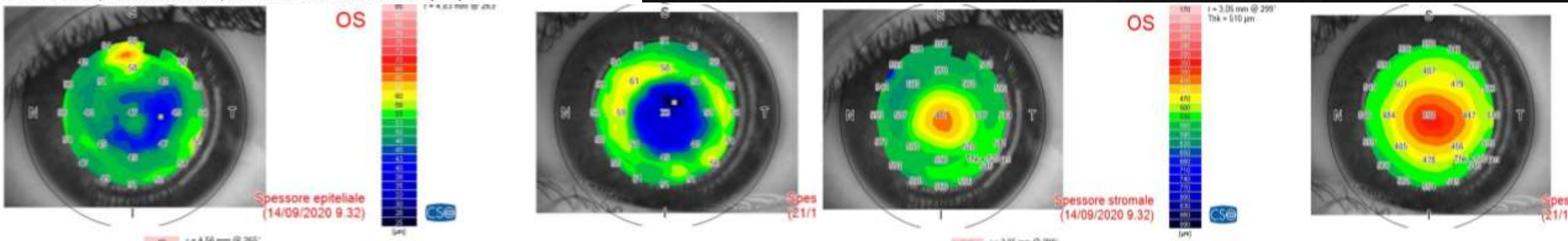
Epithelial and stromal remodelling following femtosecond laser–assisted stromal lenticule addition keratoplasty (SLAK) for keratoconus

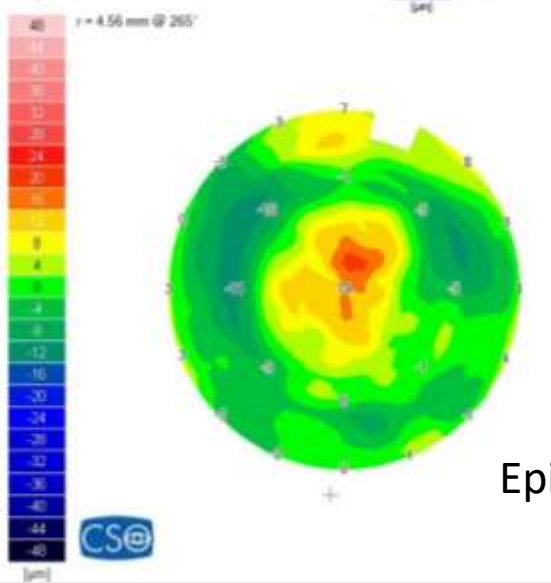
scientific reports 2021

Mario Nubile[1], Niccolò Salgari[1✉], Jodhbir S. Mehta[2], Roberta Calienno[1], Emanuele Erroi[1], Jessica Bondi[1], Manuela Lanzini[1], Yu-Chi Liu[2] & Leonardo Mastropasqua[1]

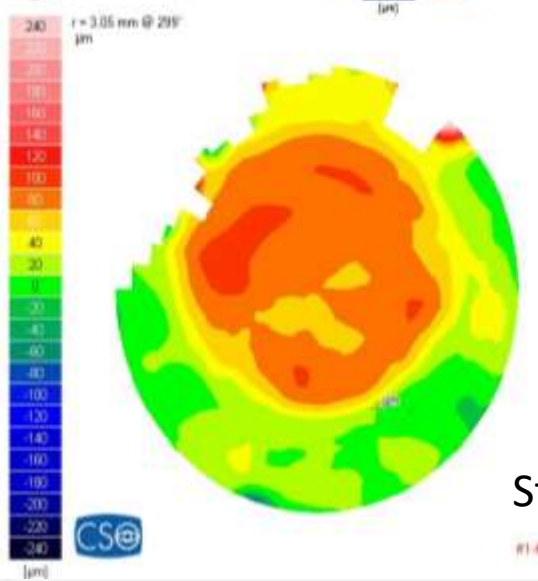


Intrastromal lenticules implantation in SLAK promotes corneal reshaping, characterized by central flattening and both stromal thickening and epithelial thickness restoration.





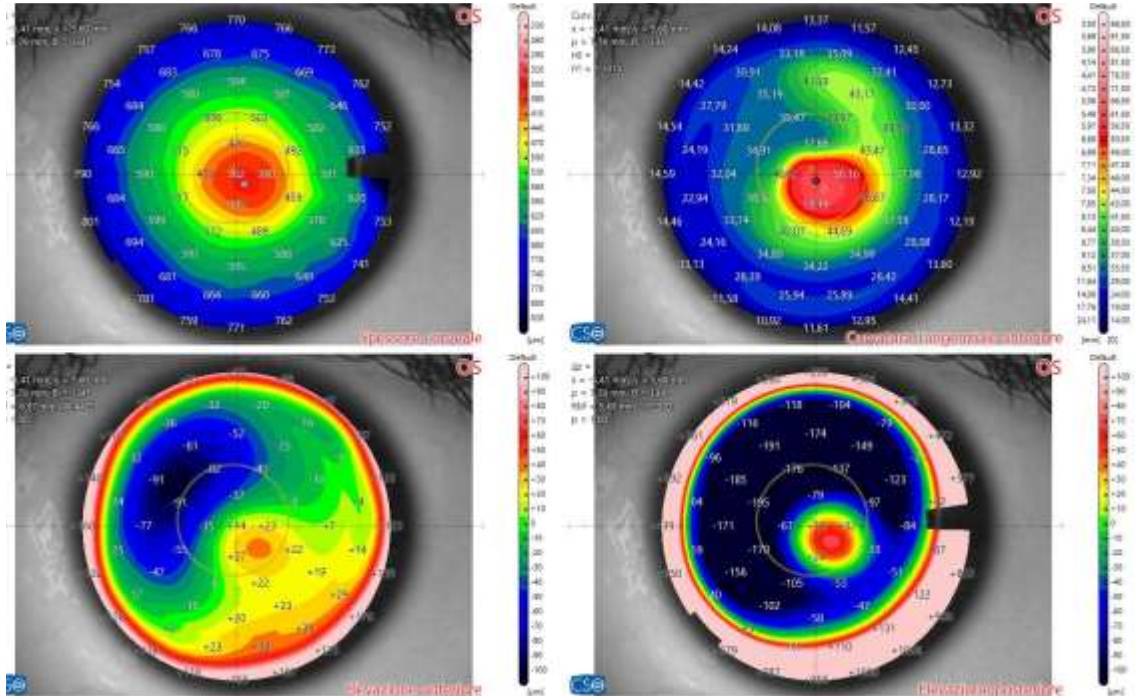
Epithelial thickness

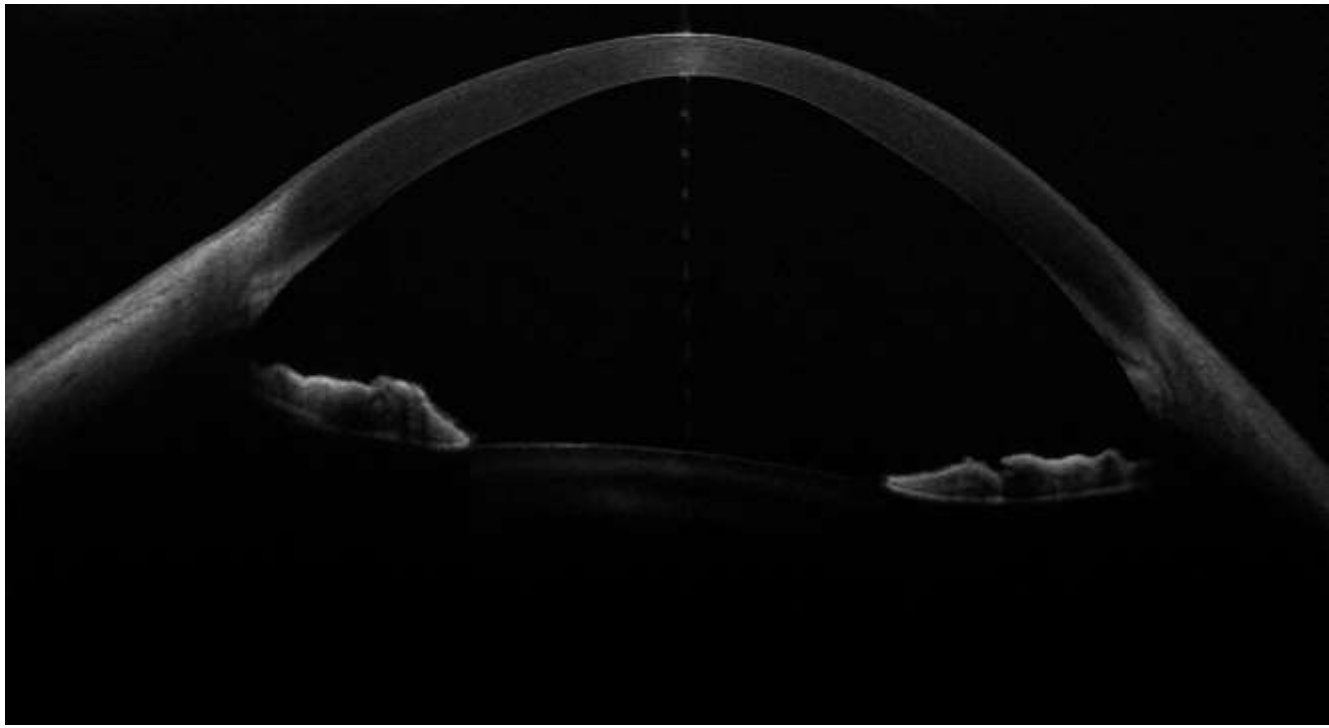


Stromal thickness

SLAK in Post-SMILE Ectasia

Clinical example cases: Pre Operative

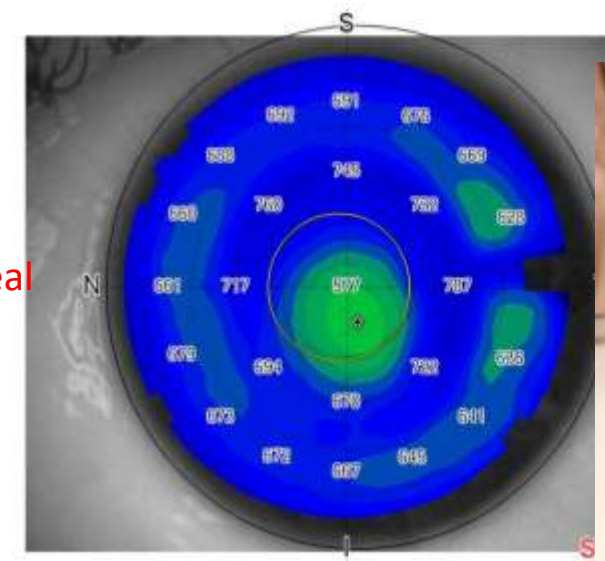


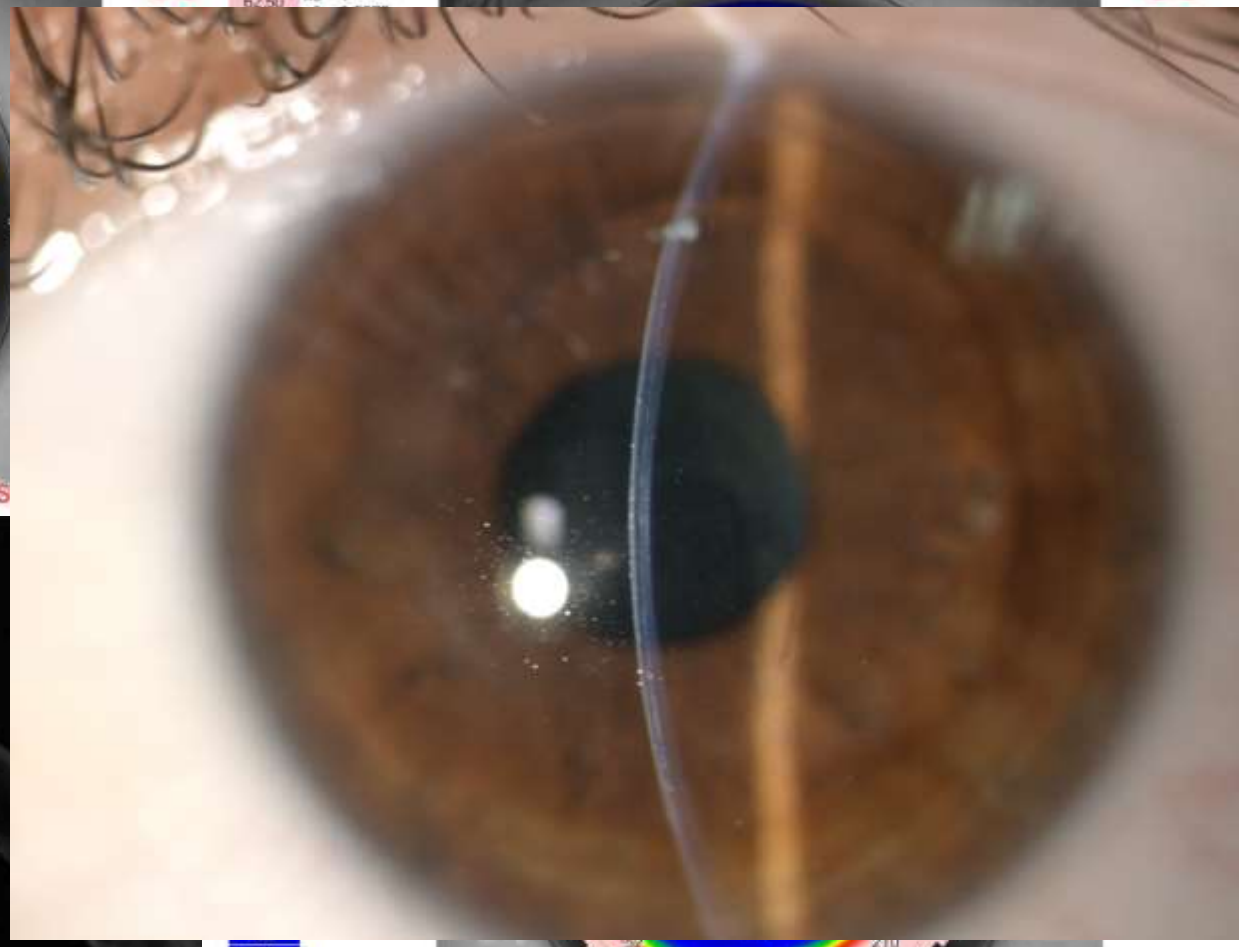


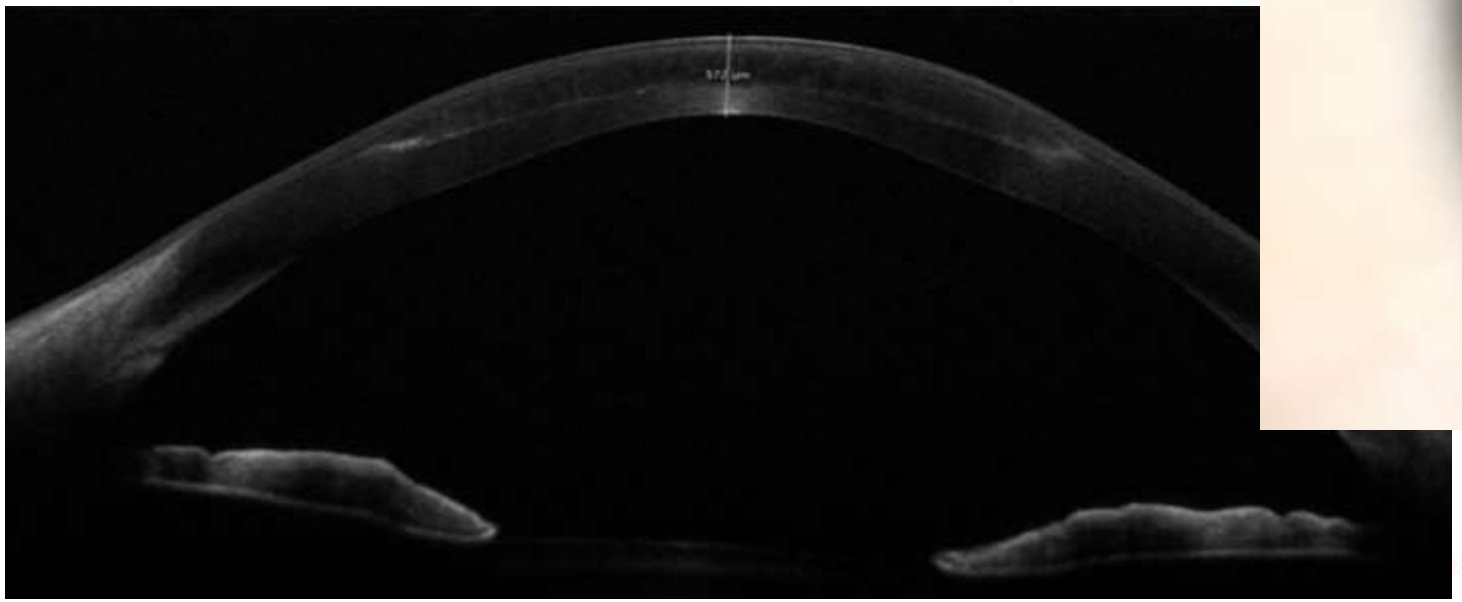
SLAK in post-SMILE ectasia: clinical case (6 months post)

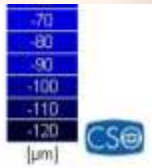
6 months post SLAK SE -6
UCVA 20/63
BCVA 20/32

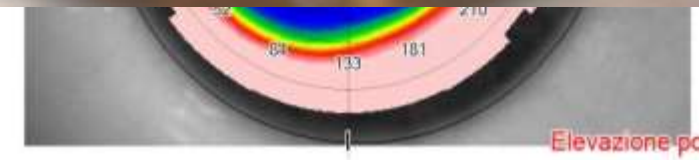
- ✓ Significant reduction of central corneal curvature and elevation
- ✓ Improvement of residual SE and UCVA/BCVA
- ✓ Significant improvement of CCT







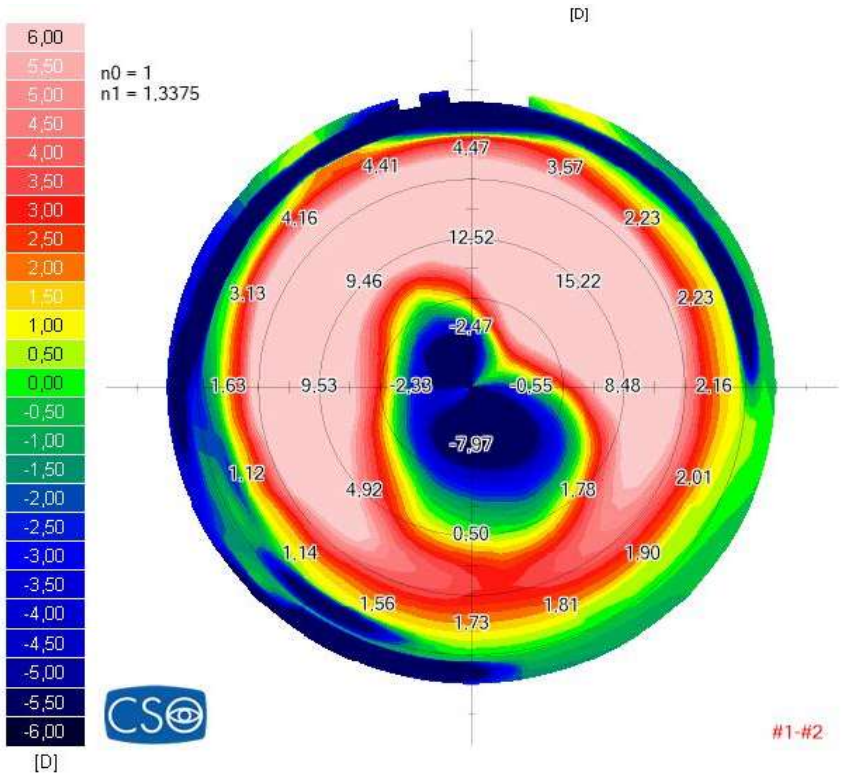




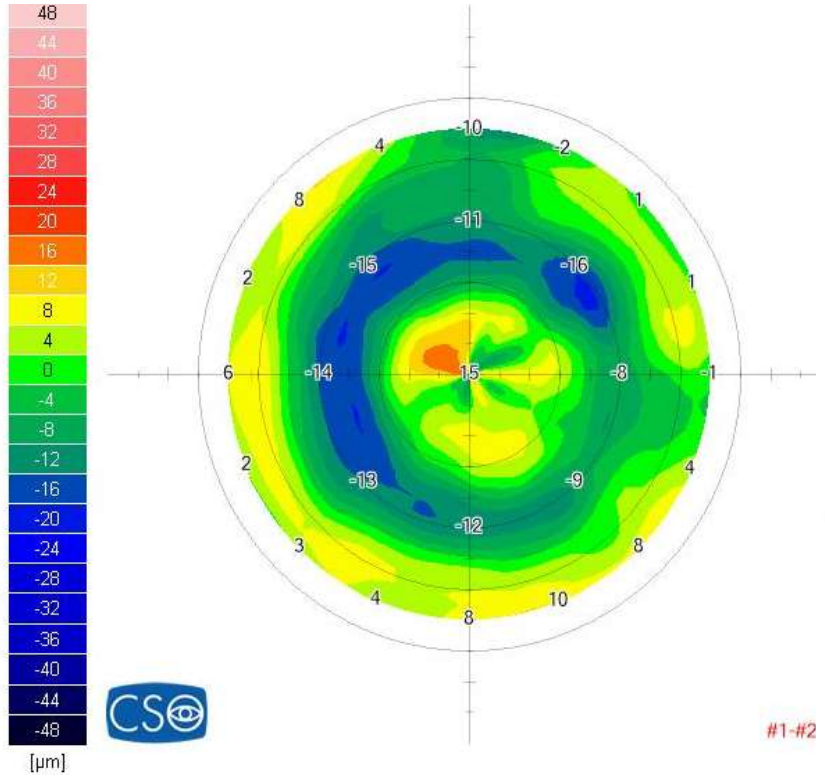
Post-SMILE ectasia: Restoring thickness by re-implanting a positive meniscus lenticule similar to the one removed at the time of surgery

SLAK in post-SMILE ectasia: clinical case (post)

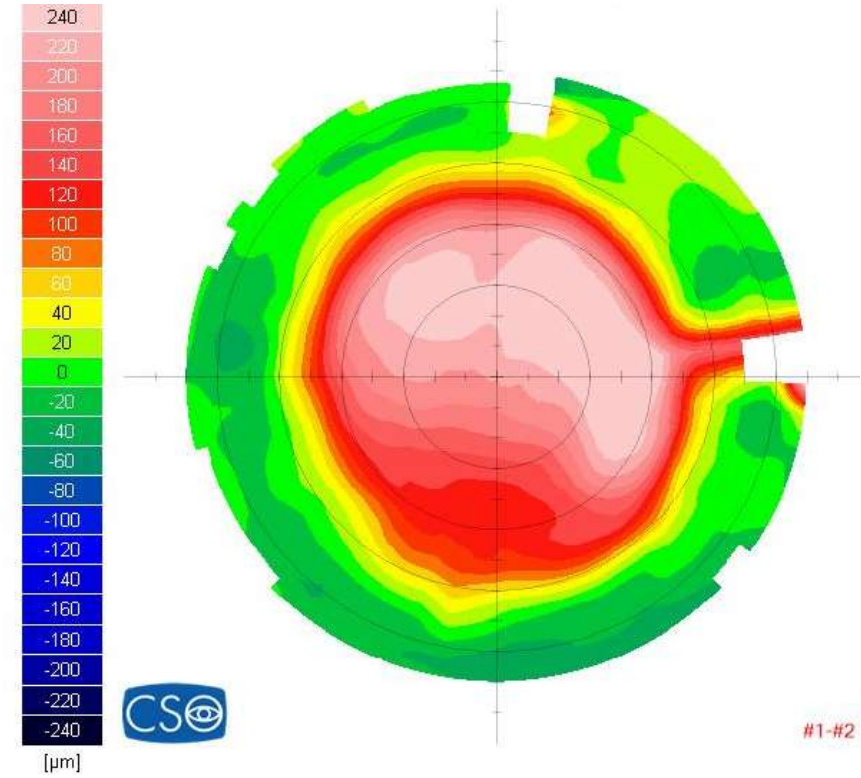
Differential map anterior curvature

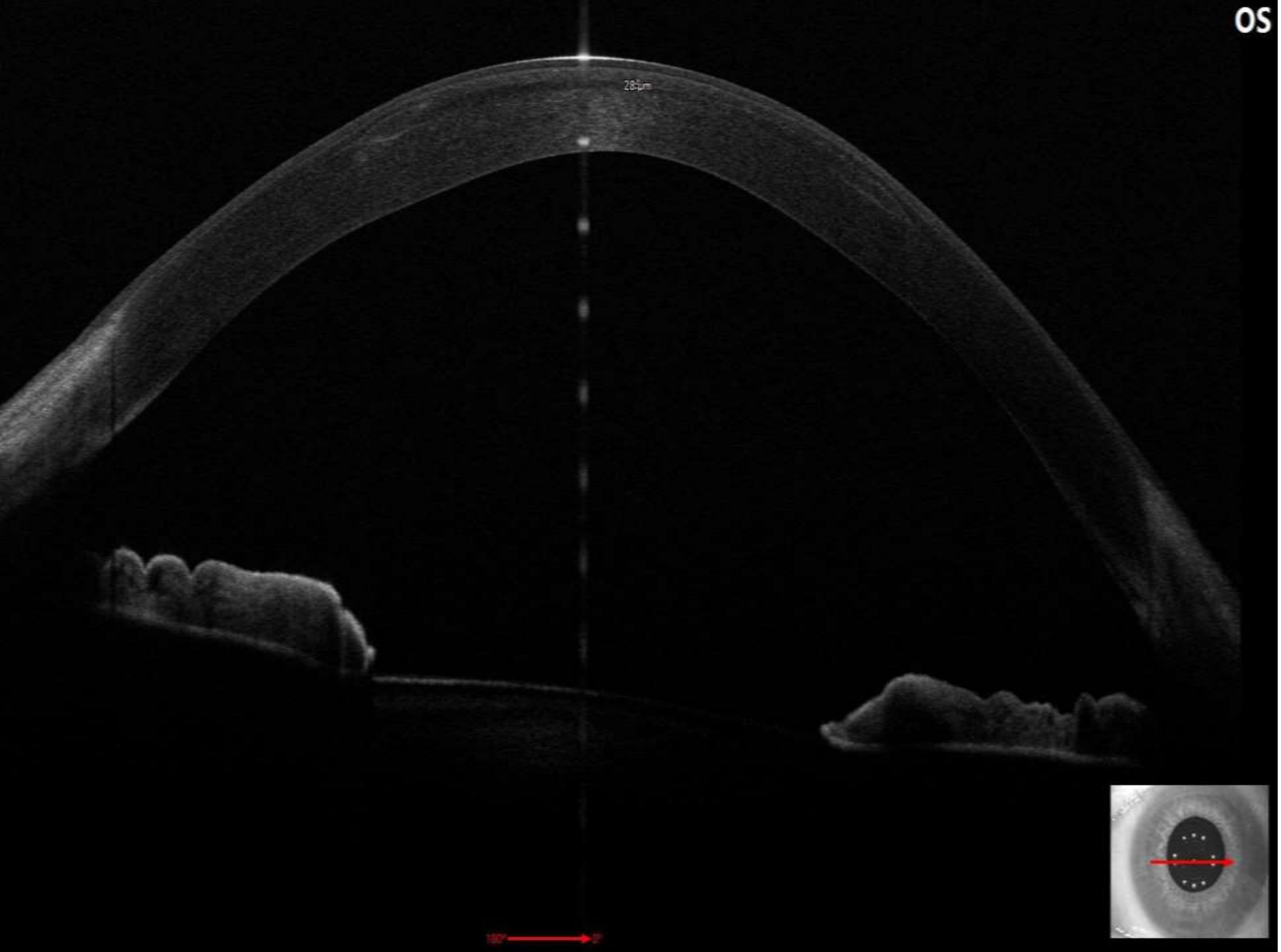


Differential map epithelial thickness



Differential map stromal thickness





SLAK in KK

5 years follow-up

BCVA pre-surgery: 20/50
sph -1,75 cyl -3,75 ax 105°

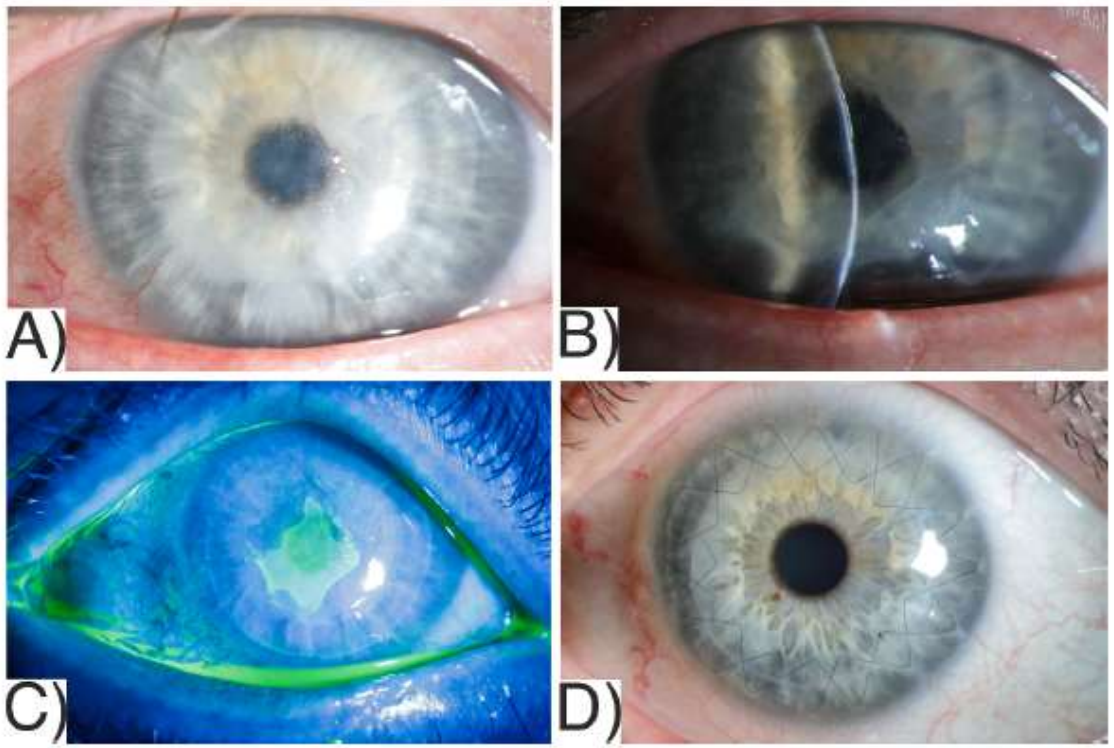
BCVA post-surgery: 20/20
sph -0,50 cyl -1,50 ax 95°

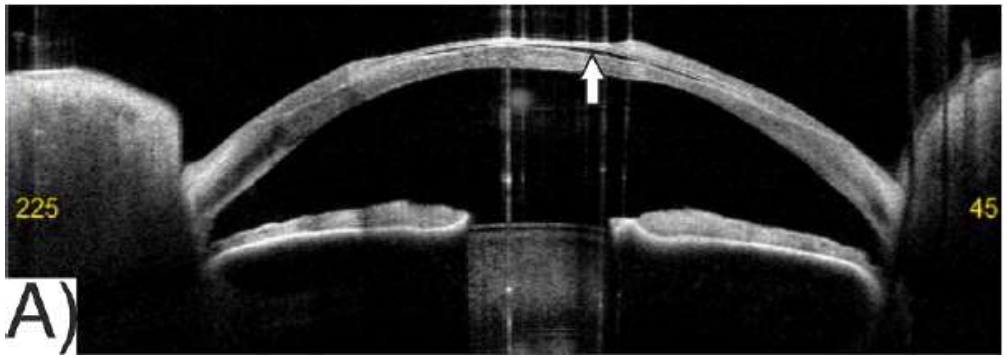
Severe ulcerative keratopathy following implantation of an acellular porcine corneal stromal lenticule in a patient with keratoconus

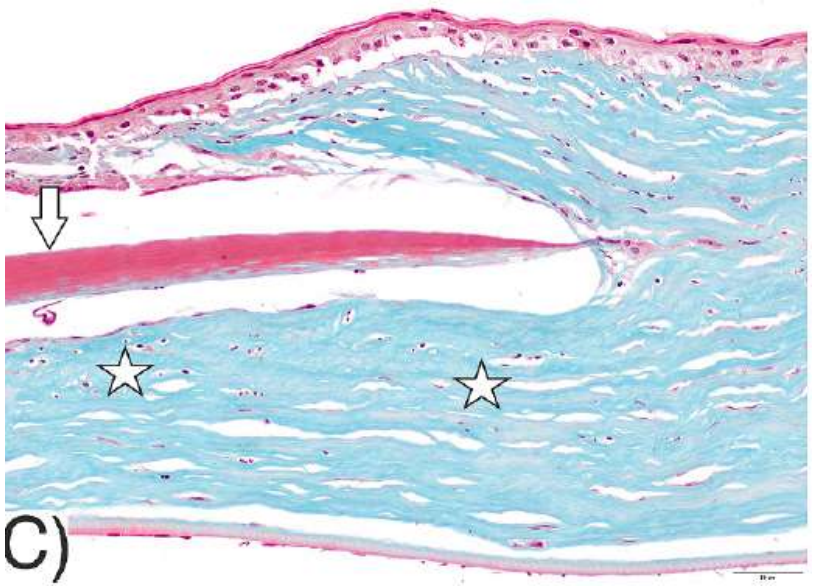
Tim Berger [a,*], Ursula Schlötzer-Schrehardt [b], Fidelis Flockerzi [c], Loay Daas [a], Elias Flockerzi [a], Berthold Seitz [a]

[a] Department of Ophthalmology, Saarland University Medical Center, Homburg, Saar, Germany
[b] Department of Ophthalmology, University of Erlangen-Nürnberg, Erlangen, Germany
[c] Institute of Pathology, Saarland University Medical Center, Homburg, Saar, Germany

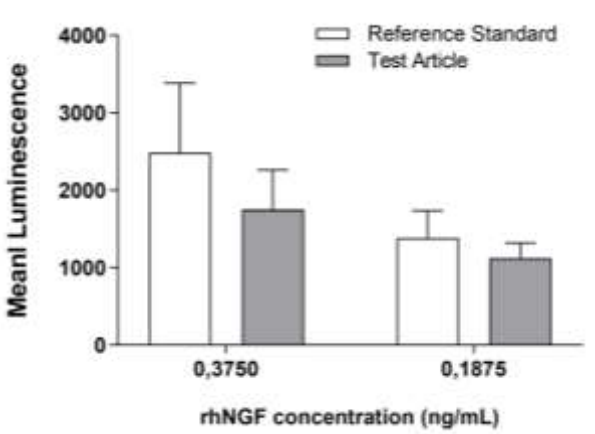
2024

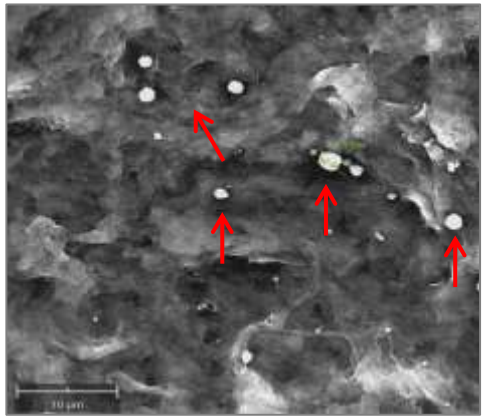


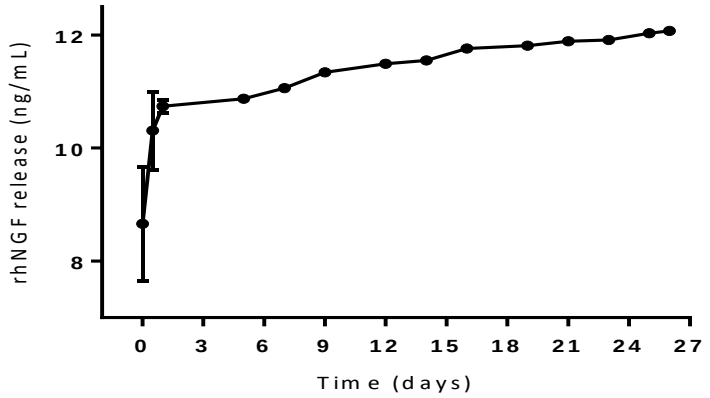


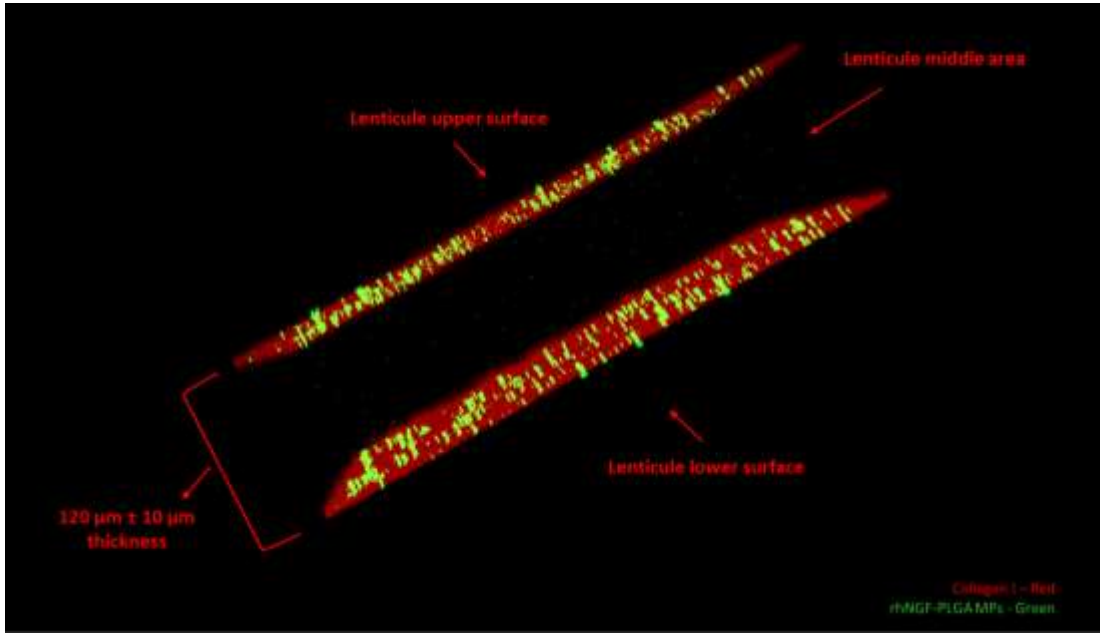


Bioengineering of human stromal lenticules: the new frontier









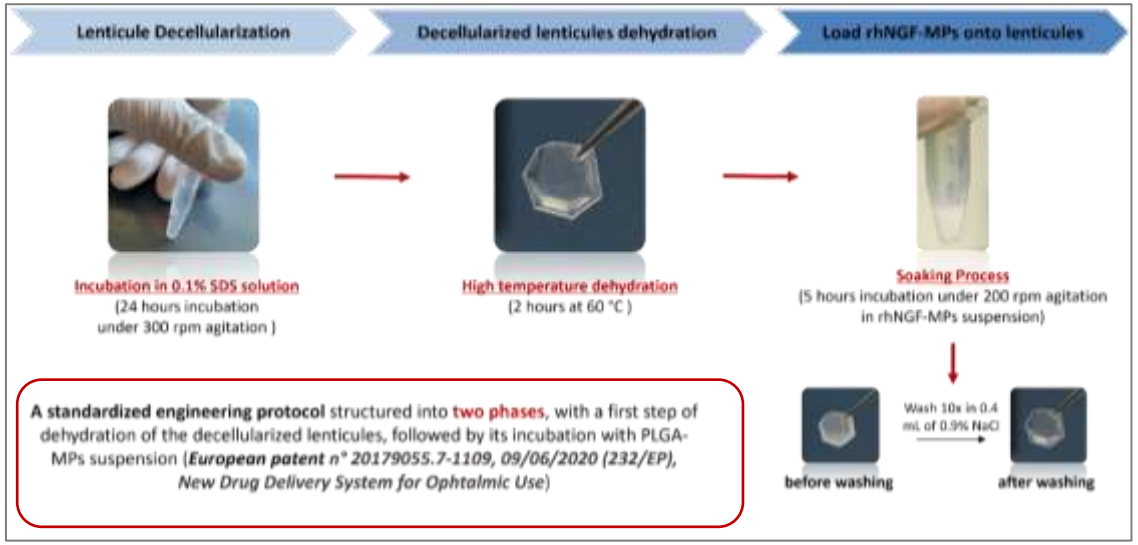
hCLs engineered with rhNGF-microparticles (rhNGF-MPs)

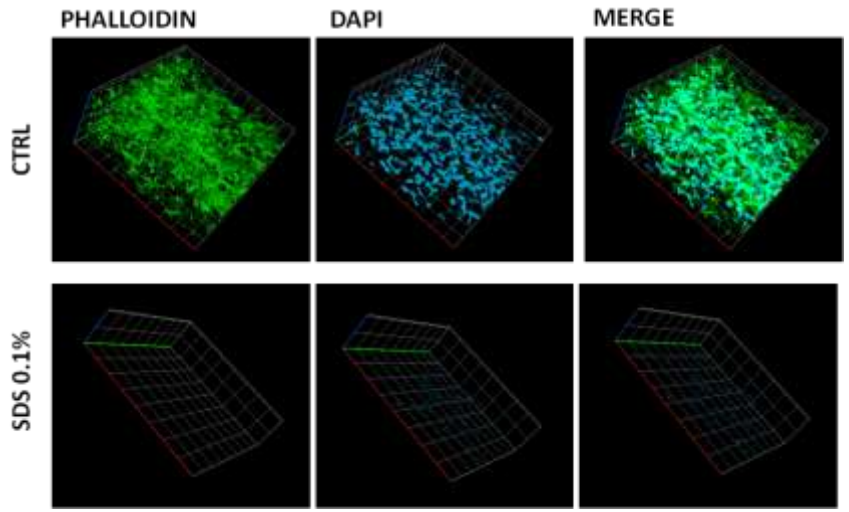

frontiers | Frontiers in Bioengineering and Biotechnology

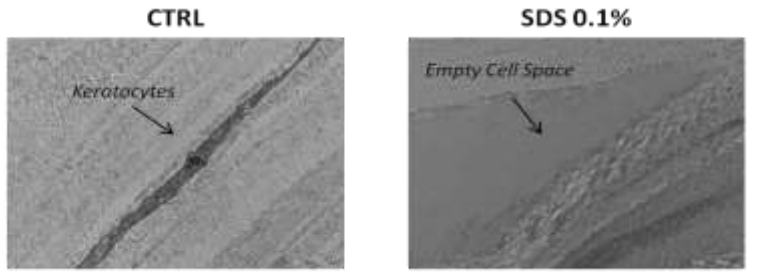
ORIGINAL RESEARCH

Bioengineered Human Stromal Lenticule for Recombinant Human Nerve Growth Factor Release: A Potential Biocompatible Ocular Drug Delivery System

Leonardo Mastropasqua[†], Mario Nubile[†], Giuseppina Acerra[2], Nicola Detta[2], Letizia Pelusi[3], Manuela Lanzini[1], Simone Mattioli[2], Manuela Santalucia[3], Laura Pietrangelo[4], Marcello Allegretti[5], Harminder S. Dua[6], Jodhbir S. Mehta[7], Assunta Pandolfi[3]† and Domitilla Mandatori[3]†



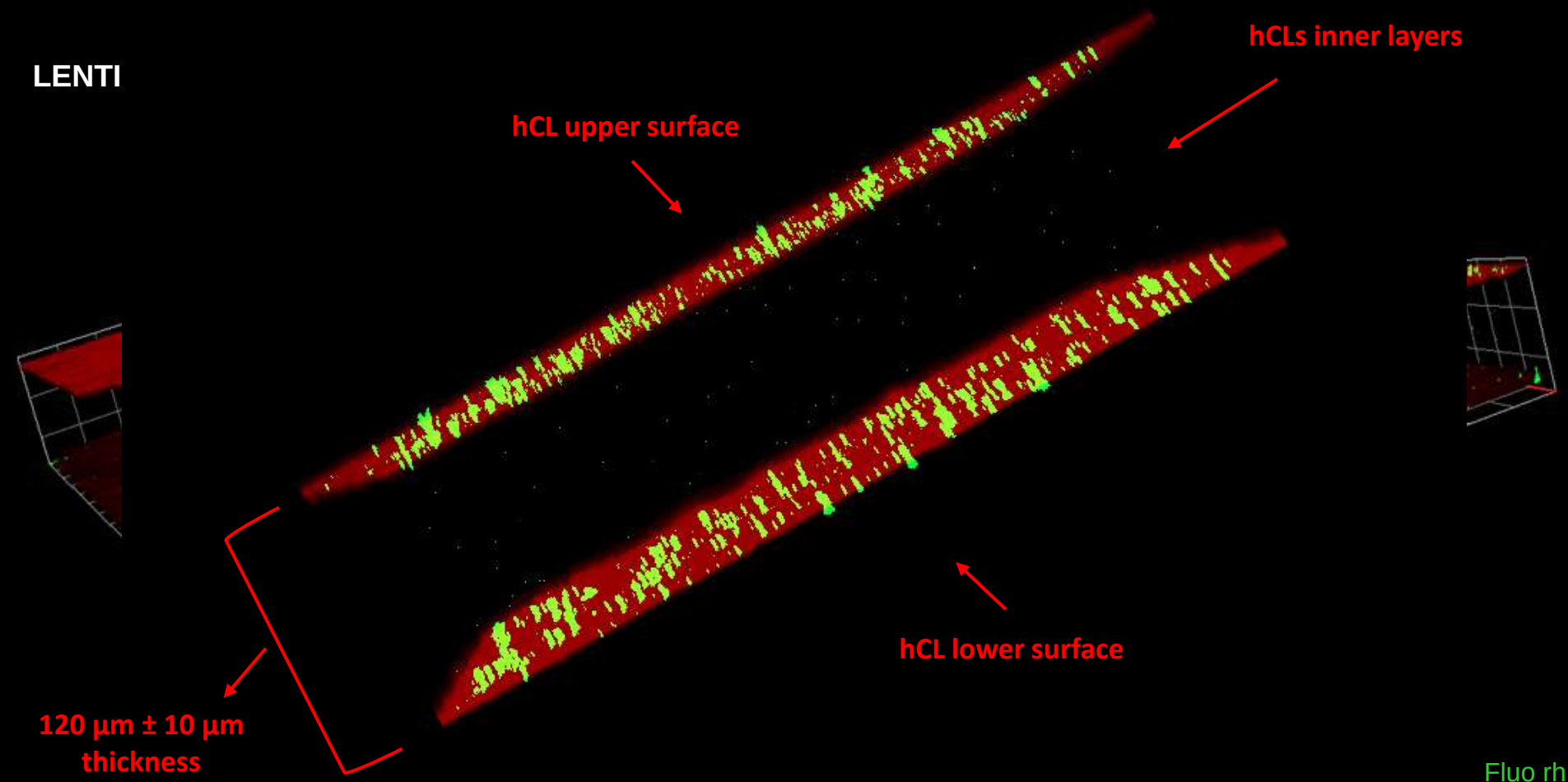




	Fibril density/ mμ²	Fibril size (nm)	Partially organized fibers (%)	Highly organized fibers (%)	Disorganized fibers (%)
CTRL	174.4 ± 5.0	25.6 ± 2.7	13.1 ± 6.1	85.4 ± 4.0	1.5 ± 2.1
SDS 0.1%	192.6 ± 20.5	24.5 ± 3.4	11.8 ± 3.5	87.0 ± 5.2	1.2 ± 1.7

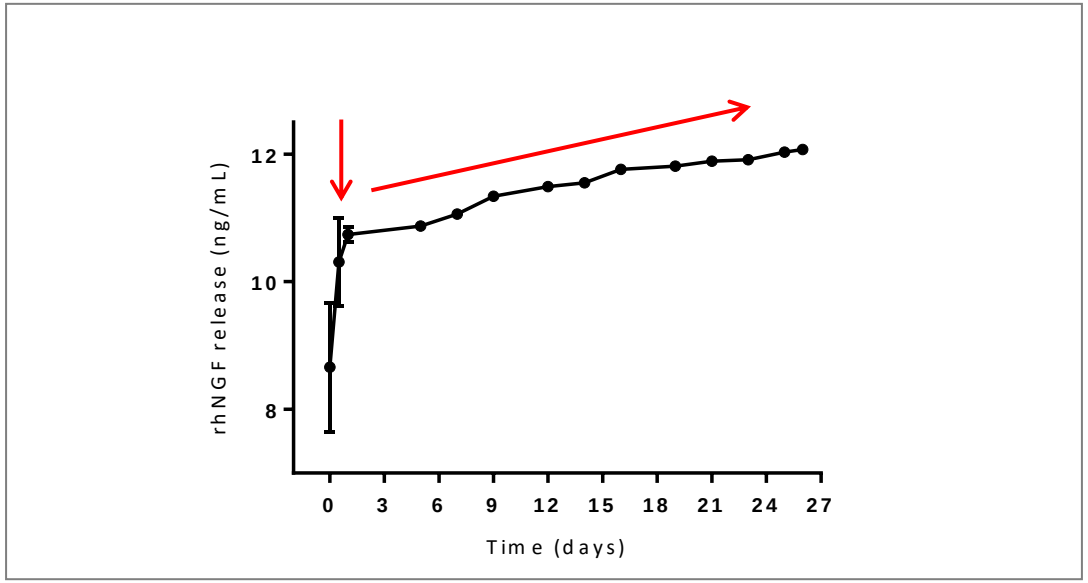
Mastropasqua L and Nubile M et al, Frontiers in Bioeng and Biotech 2022

hCLs engineered with rhNGF-microparticles (rhNGF-MPs)



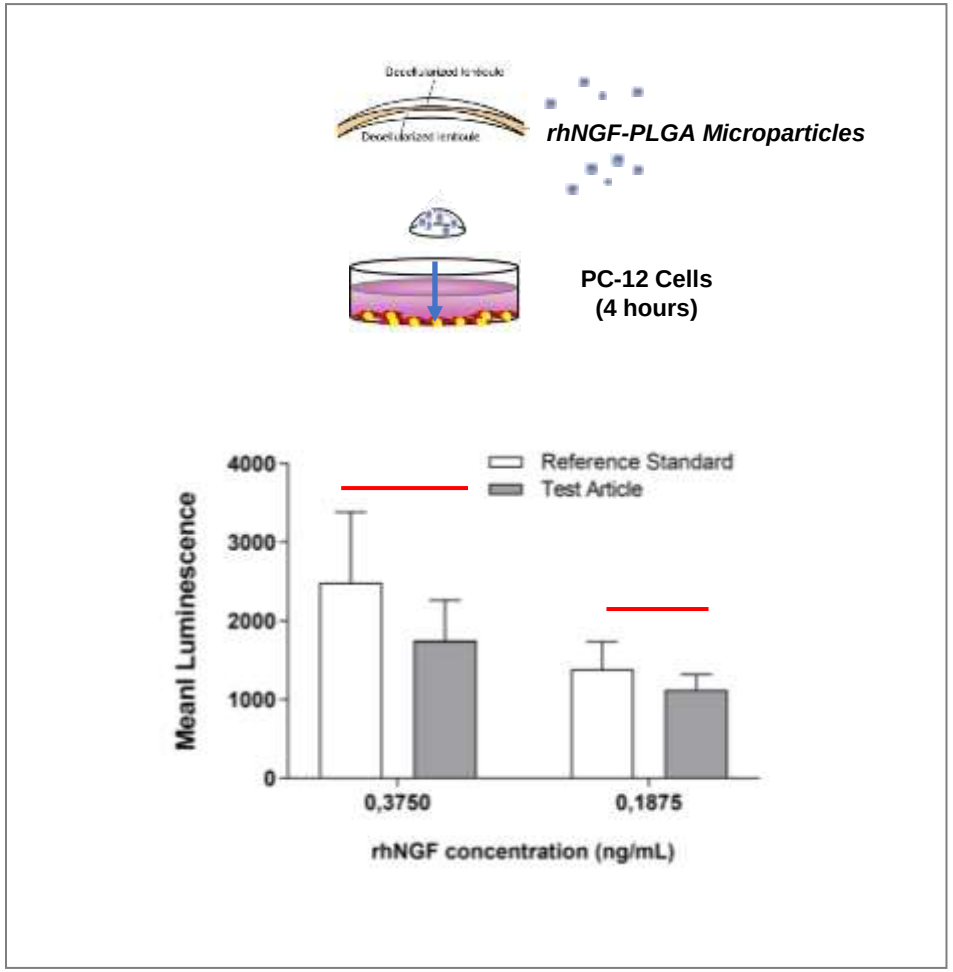
Mastropasqua L and Nubile M et al, Frontiers in Bioeng and Biotech 2022

hCLs engineered with rhNGF-microparticles (rhNGF-MPs)



In vitro **kinetic release of rhNGF from engineered decellularized hCLs**

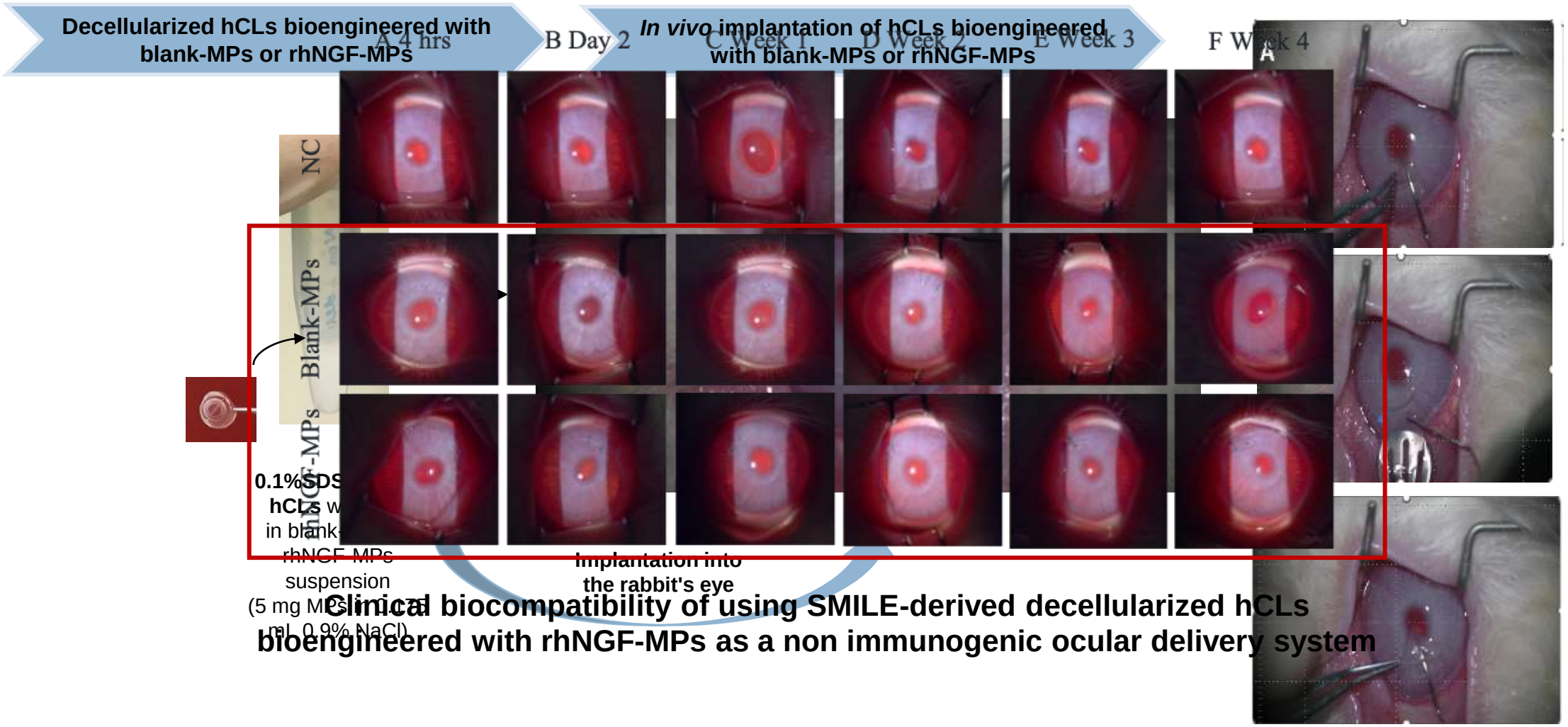
In vitro **biological activity of rhNGF released from engineered decellularized hCLs**



Mastropasqua L and Nubile M et al, Frontiers in Bioeng and Biotech 2022

RESULTS *IN VIVO* (I)

In vivo implantation of rhNGF-MPs bioengineered hCLs

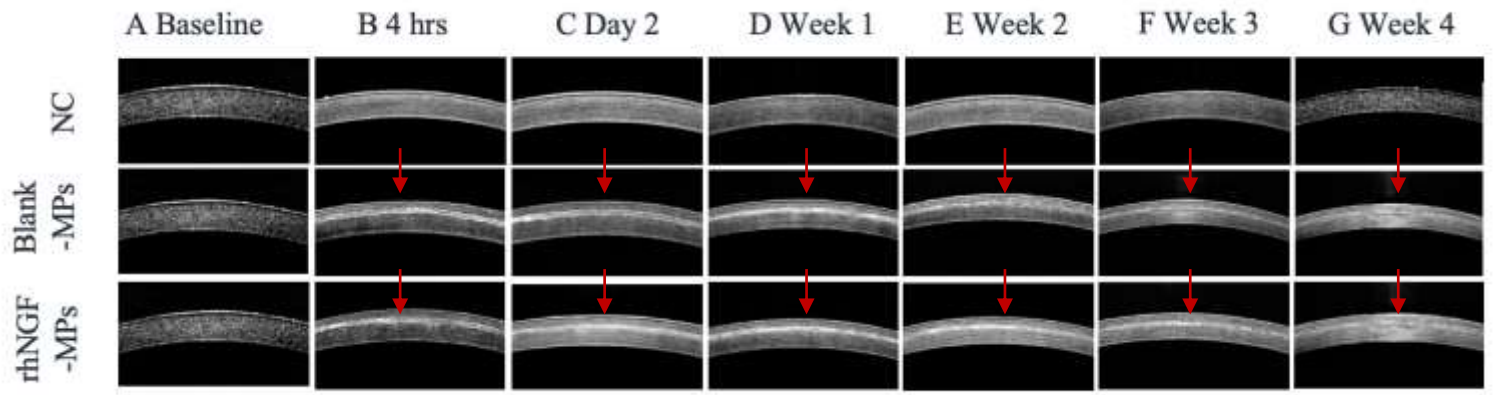


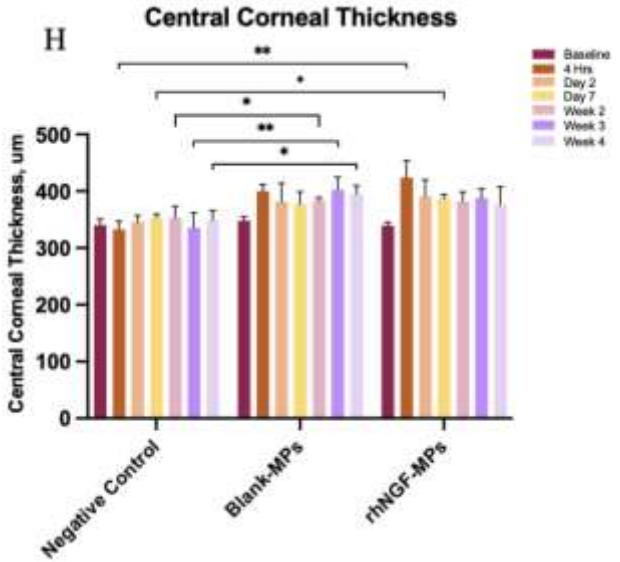
Clinical biocompatibility of using SMILE-derived decellularized hCLs bioengineered with rhNGF-MPs as a non immunogenic ocular delivery system

Unpublished data

RESULTS *IN VIVO* (II)

Central Corneal Thickness – Anterior Segment Opthical Coherence Tomography (ASOCT)





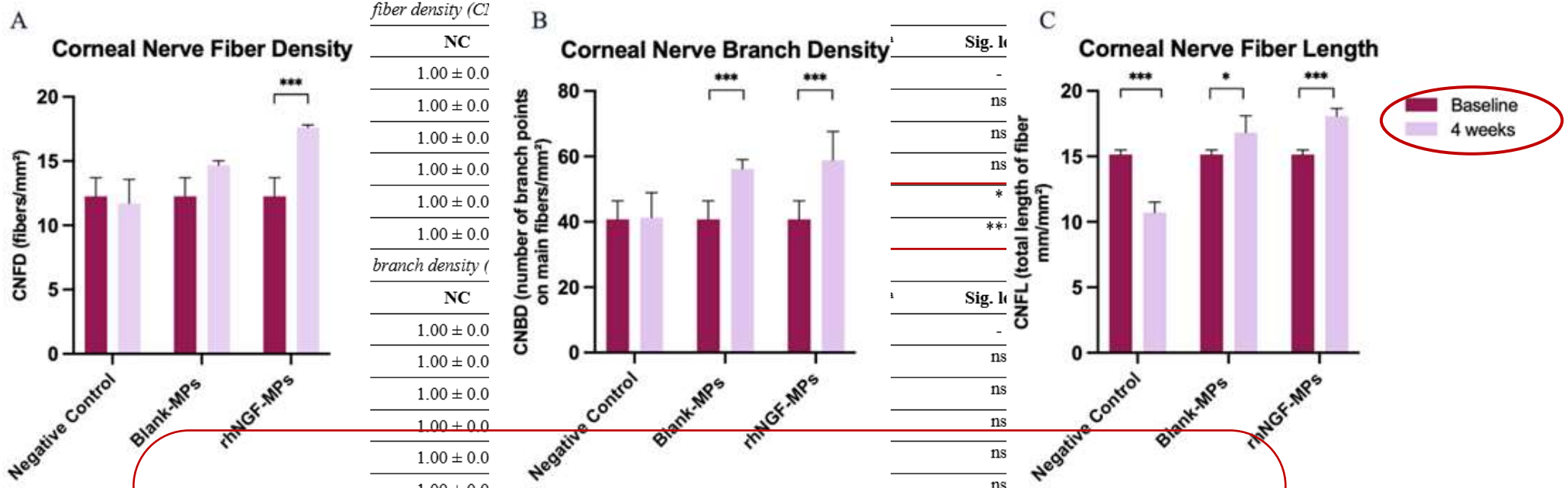
Time point	NC	Blank-MPs	rhNGF-MPs	*p*-value[a]	Sig. level
Baseline	1.00 ± 0.00	1.02 ± 0.02	1.00 ± 0.02	0.384	ns
4 hrs	1.00 ± 0.00	1.20 ± 0.04	1.26 ± 0.09	0.267	ns
Day 2	1.00 ± 0.00	1.10 ± 0.09	1.14 ± 0.08	> 0.999	ns
Day 7	1.00 ± 0.00	1.07 ± 0.06	1.10 ± 0.05	0.888	ns
Week 2	1.00 ± 0.00	1.09 ± 0.03	1.08 ± 0.05	> 0.999	ns
Week 3	1.00 ± 0.00	1.20 ± 0.06	1.15 ± 0.05	0.427	ns
Week 4	1.00 ± 0.00	1.13 ± 0.04	1.09 ± 0.08	0.361	ns

[a]Comparisons between the blank-MPs group and the rhNGF-MPs group

Unpublished data

RESULTS *IN VIVO* (III)

Corneal Nerve Regeneration – *In Vivo* Confocal Microscopy (IVCM)



fiber density (C

NC
1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0

branch density (

NC
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1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0
1.00 ± 0.0
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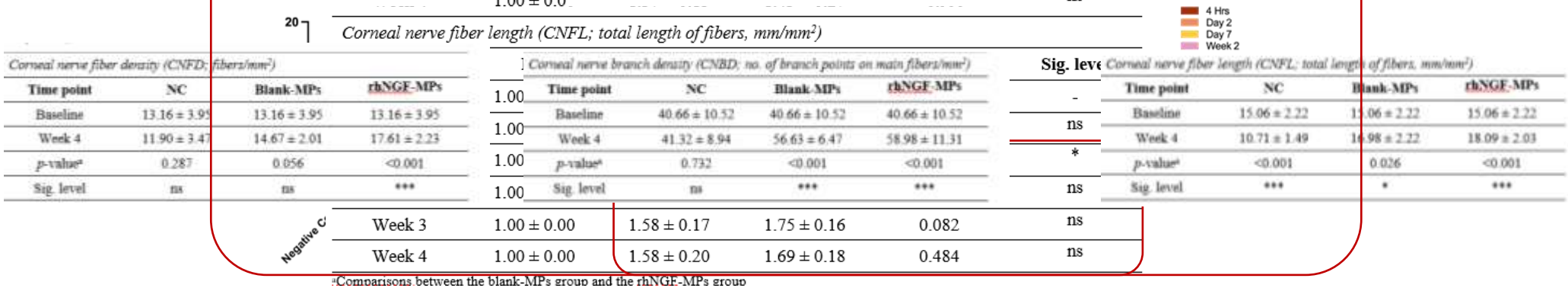

Corneal nerve fiber density (CNFD; fibers/mm²)

Time point	NC	Blank-MPs	rhNGF-MPs
Baseline	13.16 ± 3.9	13.16 ± 3.95	13.16 ± 3.95
Week 4	11.90 ± 3.47	14.67 ± 2.01	17.61 ± 2.23
p-value[a]	0.287	0.056	<0.001
Sig. level	ns	ns	***

Corneal nerve branch density (CNBD; no. of branch points on main fibers/mm²)

Time point	NC	Blank-MPs	rhNGF-MPs
Baseline	40.66 ± 10.52	40.66 ± 10.52	40.66 ± 10.52
Week 4	41.32 ± 8.94	56.63 ± 6.47	58.98 ± 11.31
p-value[a]	0.732	<0.001	<0.001
Sig. level	ns	***	***

Sig. leve
-
ns
*
ns

Corneal nerve fiber length (CNFL; total length of fibers, mm/mm²)

Time point	NC	Blank-MPs	rhNGF-MPs
Baseline	15.06 ± 2.22	15.06 ± 2.22	15.06 ± 2.22
Week 4	10.71 ± 1.49	16.98 ± 2.22	18.09 ± 2.03
p-value[a]	<0.001	0.026	<0.001
Sig. level	***	*	***

Negative C	Week 3	1.00 ± 0.00	1.58 ± 0.17	1.75 ± 0.16	0.082	ns
	Week 4	1.00 ± 0.00	1.58 ± 0.20	1.69 ± 0.18	0.484	ns

[a]Comparisons between the blank-MPs group and the rhNGF-MPs group

Unpublished data

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Review | Open access | Published: 13 February 2019

Novel stem cell and gene therapy in diabetic retinopathy, age related macular degeneration, and retinitis pigmentosa

Parker E. Ludwig, S. Caleb Freeman & Adam C. Janot

International Journal of Retina and Vitreous 5, Article number: 7 (2019) | Cite this article

STEM CELLS

Regenerative Medicine | Open Access

Neuroprotective Effects of Human Mesenchymal Stem Cells and Platelet-Derived Growth Factor on Human Retinal Ganglion Cells

Andrew Osborne, Julie Sanderson, Keith R. Martin

MINI REVIEW

Sustained Delivery System for Stem Cell-Derived Exosomes

Andri K. Riau [1], Hon Shing Ong [1,2,3], Gary H. F. Yam [1,2] and Jodhbir S. Mehta [1,2,3]**

International Journal of Molecular Sciences

MDPI

urrent Trends and Future Perspective of lesenchymal Stem Cells and Exosomes in orneal Diseases

ssan Mansoor [1,2,3], Hon Shing Ong [1,3], Andri K. Riau [1], Tisha P. Stanzel [1,†], hbir S. Mehta [1,3,4,5,*] and Gary Hin-Fai Yam [1,4,*]

Experimental Eye Research

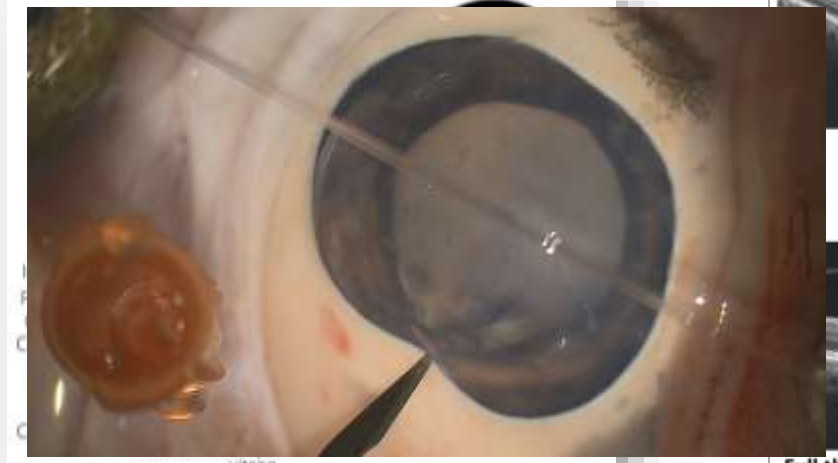
ELSEVIER

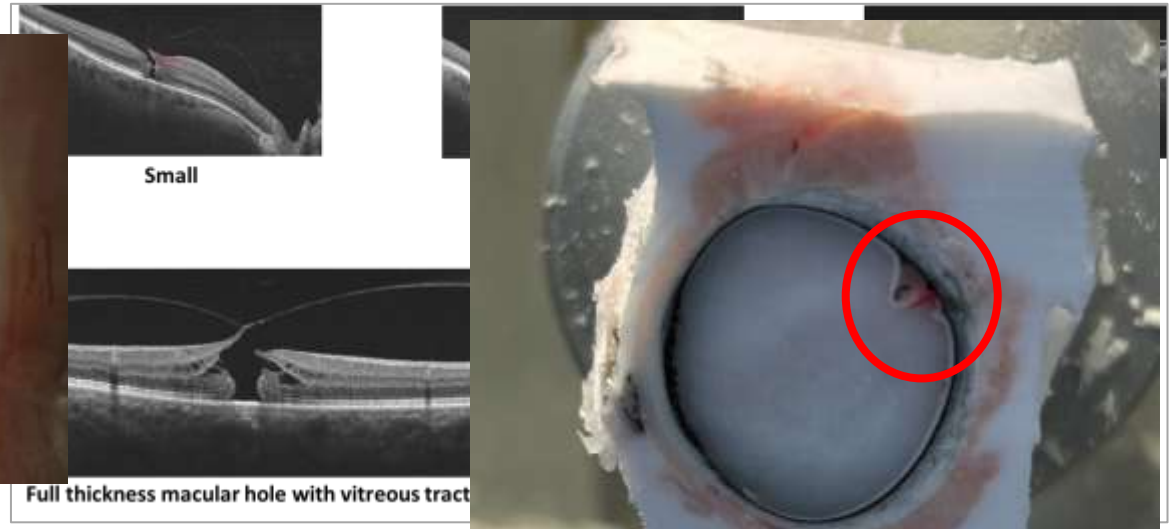
Safety of grafting acellular human corneal lenticule seeded with Wharton's Jelly-Derived Mesenchymal Stem Cells in an experimental animal model

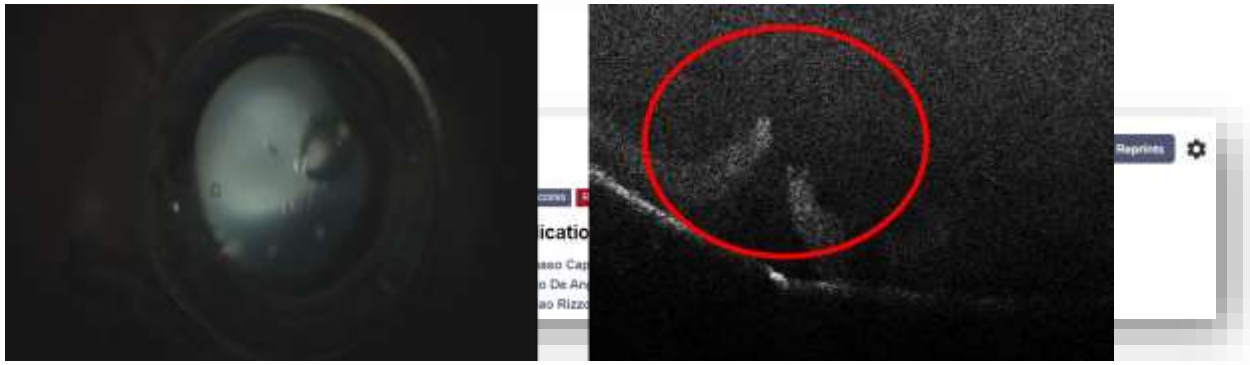
Hossein Aghamollaei, Hesam Hashemian, Hamidreza Safabakhsh, Rabeleh Halabian, Mahdi Baghersad, Khosrow Jadidi

Unpublished data

EX VIVO MACULAR HOLE MODEL







Implanted hCL stained with eosin on macular hole damaged porcine eye

Unpublished data

Domitilla Mandatori, Rodolfo Matropasqua, M. Nubile

Possible therapeutic applications

RhNGF microparticles embedded in decellularized lenticules is an efficient method to achieve **greater concentrations of drug substances, for an extended period of time**, in diseased corneas, paving the way for **combined surgical and medical therapy**

Hypothetically, **every kind of eye drug substances can be included in such lenticules**, not only for corneal therapy, but also for other ocular diseases

SMILE derived lenticules (from over 6 milion refractive procedures, as in 2022) can drastically **improve the shortage of transplantable corneal tissues** and can be **stored** in eye banks

A crucial point is proper tissue preservation, and **cryopreservation** represents a **valid method** for **long term storage** that **maintains lenticule vitality**

Creation of a lenticule bank to collect, catalog, process, cryopreserve and distribute the lenticules could be **advantageous**, **safe** and **feasible**

Cell and Tissue Banking (2022)

Preservation of corneal stromal lenticule: review

Martina Nemcokova, Jakub Dite, Yun Min Klimesova, Magdalena Netukova & Pavel Studeny

Tissue Engineering Part A

Andri K. Riau, Kenny P.Y. Boey, Nur Zahirah Binte M. Yusoff, Tze-Wei Goh, Gary H.F. Yam, Kin F. Tang, Catherine S.H. Phua, Hui-Jun Chen, Yoke F. Chiew, Yu-Chi Liu, and Jodhbir S. Mehta

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