CXL in ultra-thin corneas: **sub400 protocol**

Prof. Farhad Hafezi, MD PhD, FARVO

2009

Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas

Farhad Hafezi, MD, PhD, Michael Mrochen, PhD, Hans Peter Iseli, MD, Theo Seiler, MD, PhD

JOURN
CATAR
REFRACTIV

2014

Contact Lens-Assisted Collagen Cross-Linking (CACXL): A New Technique for Cross-Linking Thin Corneas

Soosan Jacob MS, FRCS, DNB; Dhivya Ashok Kumar, MD; Amar Agarwal, MS, FRCS, FRCOpth; Sushanth Basu, DO; Pratheek Sinha, BOptom; Ashvin Agarwal, MS

Refract
Surger

2014

Customized epithelial debridement for thin ectatic corneas undergoing corneal cross-linking: epithelial island cross-linking technique

Cosimo Mazzotta[1]
Vincenzo Ramovecchi[2]

Clinical Ophthal

Modifiying factors

Thickness

Riboflavin concentration

Modifiying factors

Thickness

Riboflavin concentration

UV fluence

Modifiying factors

Keep it simple!

UV fluence

Thickness

Riboflavin concentration

The sub400 protocol: Individualized CXL

400 µm

300 µm

The sub400 protocol: Individualized CXL

400 µm

300 µm

- hypo-osmolaric
- contact lens-assisted

The sub400 protocol: Individualized CXL

400 µm

5.4 J/cm²

3 mW/cm² for 30’

310 µm

xx J/cm²

3 mW/cm² for xx’

240 µm

xx J/cm²

3 mW/cm² for xx’

The oxygen concentration in the cornea $[CO_{oxy}]$ is determined by the amount of uptake by diffusion, the cellular oxygen consumption of the stroma Q_{cell}, the production and degradation of singlet oxygen and the oxidation of the reduced form of riboflavin:

$$[CO_{oxy}] = [CO_{air}]_0 + CO_{0_{Riboflavin\,coated}} \cdot \left(1 - e^{-\frac{2\alpha \cdot \eta_{cor}}{th}}\right) + [S_{oxy}] \cdot \left(e^{-k_{degSoxy}\Delta t} - 1\right) - [RFH_2] \cdot \left(1 - e^{\frac{k_{RFH2ox}}{k_{Qrib}} \cdot [CO_{oxy}] \cdot \left(1 - e^{-k_{Qrib} \cdot \Delta t}\right)}\right) - \frac{Q_{cell}}{22.4L} \cdot \frac{Oxy_{tension}}{160mmHg} \cdot \Delta t$$

(eq. 3)

where Δ_{oxy} is the difference in oxygen concentration between the current and the normal oxygen content in the cornea, $[S_{oxy}]$ is the concentration of singlet oxygen, $k_{degSoxy}$ is the 1st order degeneration rate constant of singlet oxygen, $[RFH_2]$ is the concentration of the reduced form of riboflavin, k_{QRib} is the quenching rate of riboflavin, k_{RFH2ox} is the oxidation rate of the reduced form of riboflavin, Q_{cell} is the stromal oxygen consumption for a given oxygen tension $Oxy_{tension}$ [15]. The oxygen tension can be calculated from the oxygen concentration $[CO_{oxy}]$, the molar mass of oxygen $M_{O_2} = 32\frac{g}{mol}$ and experimental data [8],[16]:

$$Oxy_{tension} = [CO_{oxy}] \cdot M_{O_2} \cdot \frac{102mmHg}{7.3\frac{mg}{L}} \qquad \textit{(eq. 4)}$$

[EM] is the concentration of the estimated ratio of extracellular matrix, i.e. collagen and non-collagenous proteins.

$$[EM] = \frac{0.18 \cdot \rho_{cornea}}{M_{collagen} \cdot N_A} - 400 \cdot [S_{oxy}] \cdot \left(1 - e^{-\frac{S_{degSox} \cdot [EM] \cdot \left(1 - e^{-k_{degSox} \cdot \Delta t}\right)}{k_{EMox}}}\right) \qquad \textit{(eq. 5)}$$

where $M_{collagen}$ is the molecular mass of collagen with about 407 Da ($6.76 \cdot 10^{-25}$ kg), ρ_{cornea} is the density of the cornea and 0.18 is the assumed content of collagen and non-collagenous proteins in

CXL for keratoconus

The concentration of photons in the cornea [Photon] is de

along the cornea:

$$[Photon] = \frac{I_0 \cdot \Delta t \cdot \lambda \cdot \left(1 - 10^{-\alpha th - \varepsilon [CO_{oxy}] (th + th_{RibTop})}\right)}{h \cdot c \cdot N_A \cdot th} \qquad \textit{(eq. 6)}$$

where I_0 is the nominal intensity of the UV lamp, λ is the wavelength, α is the absorption coefficient of the cornea stroma, ε is the extinction coefficient of riboflavin, th is the corneal thickness, th_{RibTop} = 50 µm is the thickness of the riboflavin film [17] on top of the cornea in the clinical setting, h is the Planck constant, c is the speed of light and N_A is the Avogadro number.

The concentration of singlet oxygen is determined by the quantum yield of riboflavin, the singlet oxygen degradation through physical and chemical quenching and the consumption of singlet oxygen during substrate oxidation:

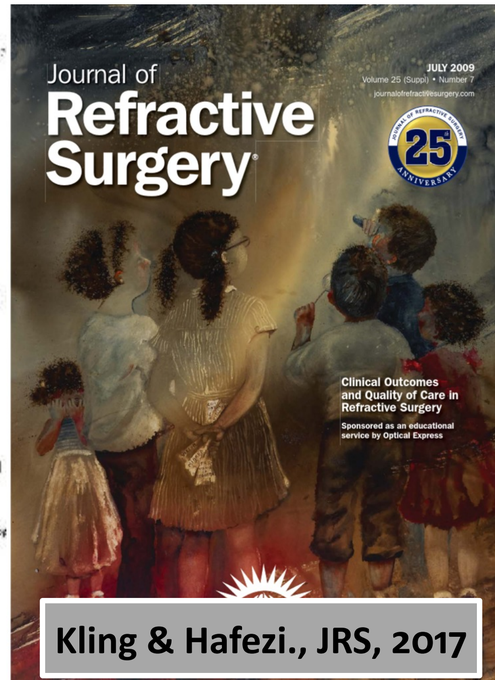
$$[S_{oxy}] = [S_{oxy}]_0 + [CO_{oxy}] \cdot \left(1 - e^{-\Phi_{Soxy} \cdot \frac{\varepsilon [CO_{oxy}] \cdot th}{\varepsilon [CO_{oxy}] (th + th_{RibTop}) - \alpha th} \cdot [Photon] \cdot \left(1 - e^{-\ldots}\right.}\right.$$

(eq. 7)

where Φ_{Soxy} is the quantum yield [18] of singlet oxygen oxidation rate of the extracellular matrix.

The concentration of the riboflavin radical [RFH·] is given

$$[RFH^{\bullet}] = [RFH^{\bullet}]_0 + [EM] \cdot \left(1 - e^{-\left(\Phi_{ISC} \cdot \Phi_{Soxy}\right)_0 \cdot \frac{\varepsilon [CO_{oxy}] \cdot th}{\varepsilon [CO_{oxy}] (th + th_{RibTop}) - \alpha \cdot th} \cdot [Ph}}\right.$$

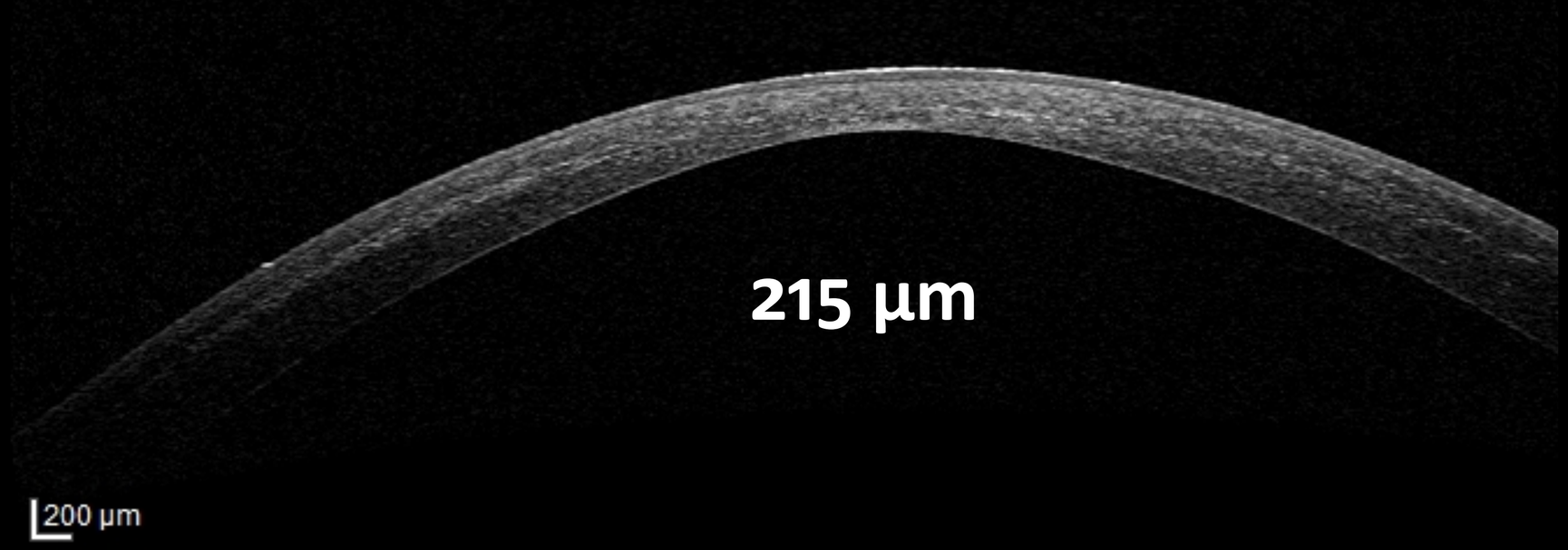


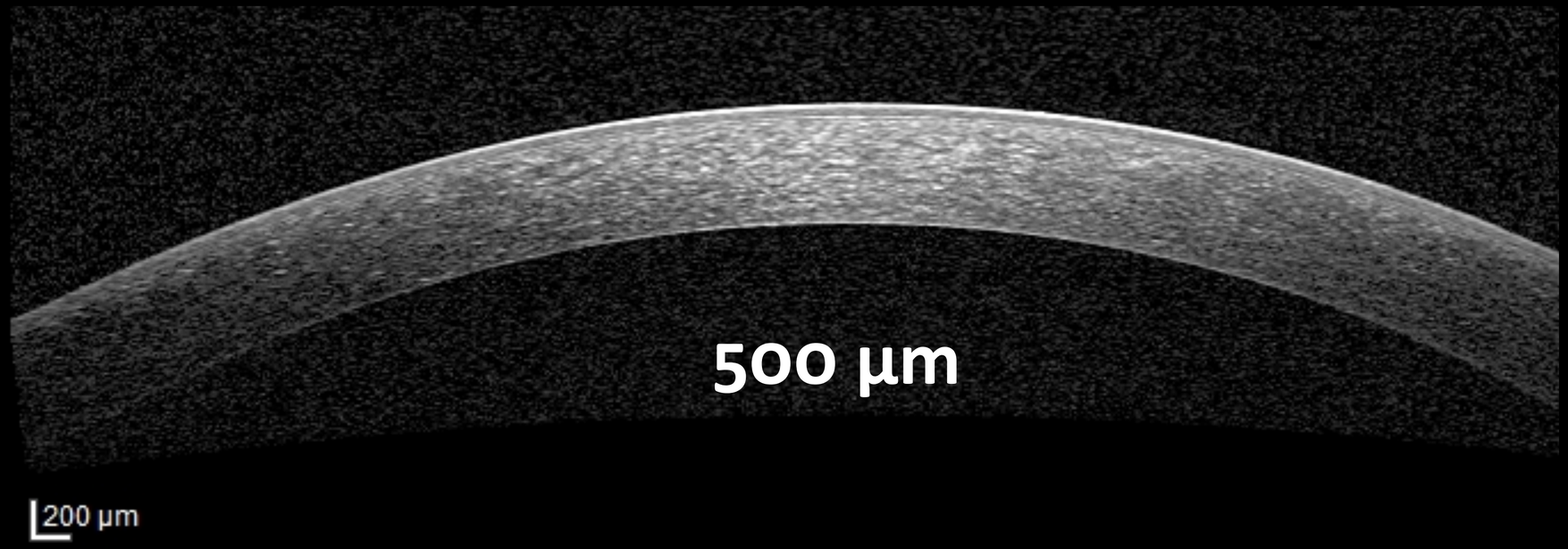
Kling & Hafezi., JRS, 2017

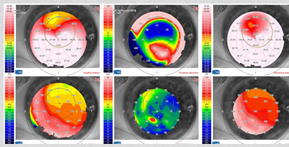
The sub400 protocol

- Prospective monocenter interventional study
- 62 eyes, progressive KC
- Treated so far: 215 μm to 395 μm
- OCT: depth of demarcation line at 1 month
- 1 year follow-up
- Success rate 85% (ultrathin corneas)
- **Baseline for entire nomogram is 10 J/cm^2**

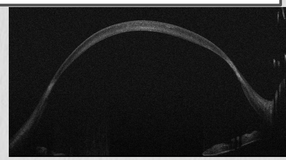
Torres et al., submitted


215 µm
200 µm

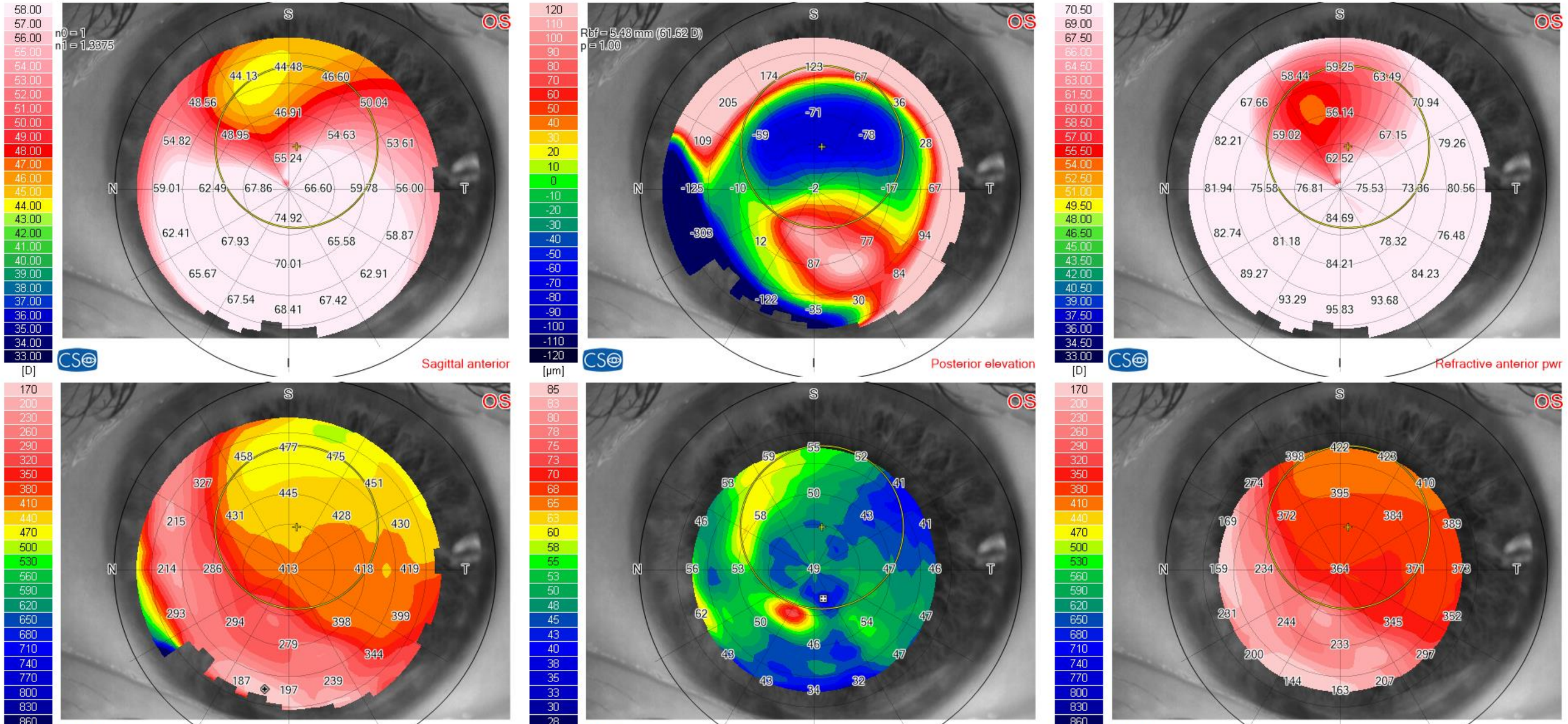

500 µm
200 µm



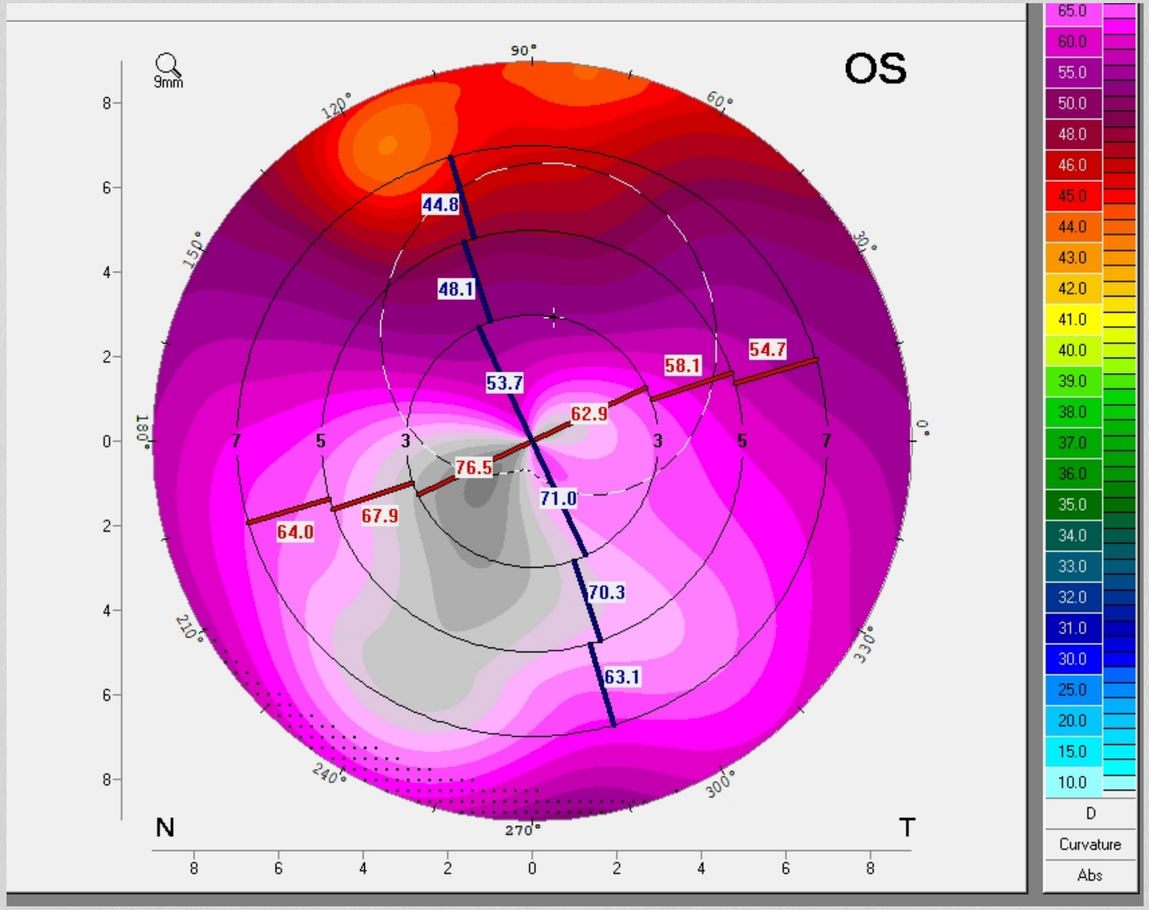
Keratoglobus: sub400

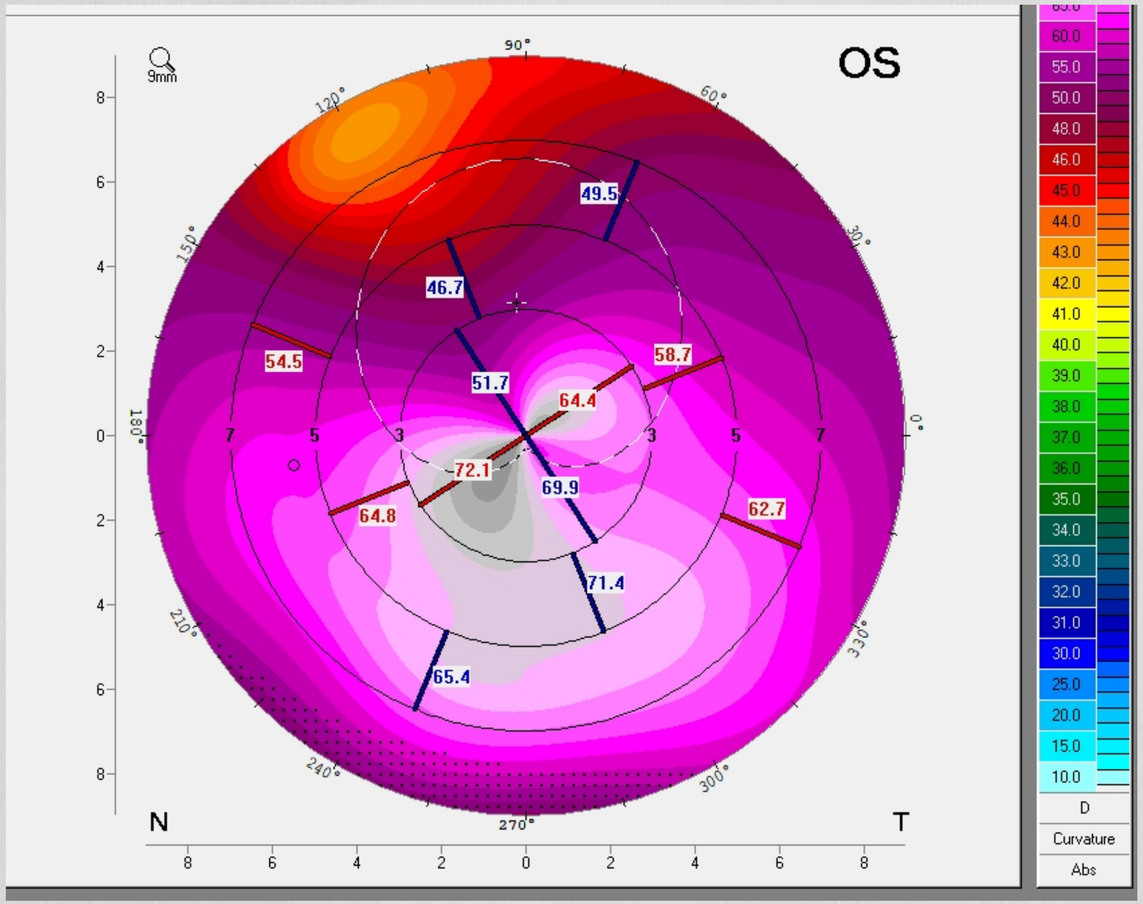


Keratoglobus: sub400



Keratoglobus: sub400





Pre CXL

2 years post CXL

ELZA

- 2019: 60 peer-reviewed papers
- All time: 602 peer-reviewed papers
- Cited in the literature: > 10’000 times
- Global PowerList: 6 mentions

Ocular Cell Biology & Biomechanics Lab - UZH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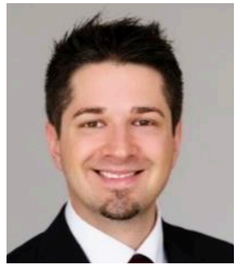
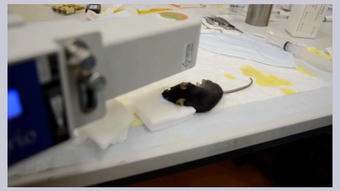
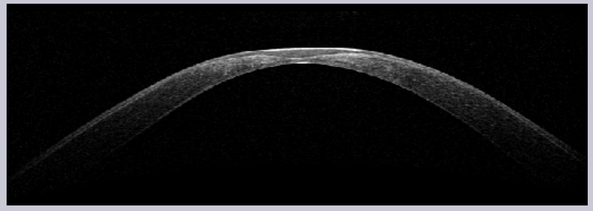

Daniel Eckert


Christian Funck

Research





Affiliations

ELZA

USC University of Southern California

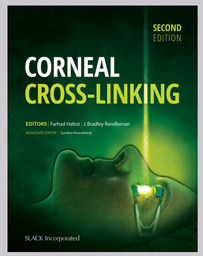
Publications

nature medicine

IOVS

nature genetics

Knowledge Transfer



International CXL 2019 Experts´ Meeting

Ocular Cell Biology & Biomechanics Lab - UZH

55
projects