A model to predict the stiffening effect of CXL: theory

Sabine Kling, PhD, Farhad Hafezi, MD,PhD
CXL efficacy as a function of corneal thickness

➔ stronger CXL in thinner corneas
Complications of strong CXL

100 μm murine cornea treated with 5.4 J/cm²

404 μm human cornea treated with 5.4 J/cm²

REF. Kling S. CXL congress (2014)

Safety of CXL treatment

- High UV absorption ➔ protection of the endothelium and crystalline lens
- Low UV absorption ➔ higher UV dose at the endothelium ➔ risk of endothelial damage ➔ risk of cataract

UV-fluence: 5.4 J/cm² with riboflavin:

Normal cornea:
- high UV absorption ➔ protection of the endothelium and crystalline lens

Thin cornea:
- low UV absorption
- higher UV dose at the endothelium ➔ risk of endothelial damage ➔ risk of cataract

UV-fluence: ~1 J/cm² with riboflavin:

400 µm

200 µm
Thin corneas

- strongly require CXL treatment
Treatment protocols for thin corneas

hypo-osmolar riboflavin to **swell** the cornea

contact lens to partially **shield** the UV light

**less effective**
How to adapt CXL for thin corneas?

- Decreasing UV irradiance
- Decreasing irradiation time
- Increasing riboflavin concentration
- Decreasing oxygen availability

• Increasing “corneal” thickness
  - Increased collagen fibril spacing
  - Reduced oxygen availability

• Decreasing UV irradiance
• Decreasing irradiation time
• Increasing riboflavin concentration
• Decreasing oxygen availability
Algorithm to predict the stiffening effect and demarcation line as a function of different CXL treatment parameters.
Lambert-Beer law of light absorption

\[ I(th) = I_0 \cdot 10^{-\left(\alpha + \varepsilon \cdot [C_{ribo}]\right) \cdot th} \]

- exponential decrease
- dependent on riboflavin concentration
Fick’s law of diffusion

Temporal diffusion of riboflavin and oxygen into the corneal stroma

Riboflavin availability below a 120 μm corneal flap

Oxygen availability below a 120 μm corneal flap

Compared to experimental data from Kamaev P., IOVS (2012)
Chemical reaction scheme

Rate of photon and singlet oxygen production

Rate of singlet oxygen interaction with the extracellular matrix

\[ RF \xrightarrow{h\nu} 1RF^* \xrightarrow{\Phi_{ISC}} 3RF^* + 3O_2 \]

\[ RFH^+ \xrightarrow{k_{qRibo}} LC \]

\[ CDRF \]

\[ RFH_2^+ \xrightarrow{k_{qRadical}} O_2 \]

\[ H_2O_2 + CMF \]

\[ EM + EM_{ox} \approx CXL \]

Riboflavin degradation

Oxygen consumption

Rate of photon and singlet oxygen production

Rate of singlet oxygen interaction with the extracellular matrix
Demarcation line prediction

Accelerated CXL produced a more shallow demarcation line than standard CXL.
Studying different CXL protocols

Irradiances: 250 $\mu$W/cm$^2$ to 18 mW/cm$^2$

Irradiation times: 30s to 30 min

UV fluences: 0.09 J/cm$^2$ to 5.4 J/cm$^2$

UV source: pulsed / continuous

Corneal thickness:
- pig ($\sim$800 $\mu$m)
- rabbit ($\sim$400 $\mu$m)
- mouse ($\sim$100 $\mu$m)
Experimental analysis

Experimental material testing:
stress-strain extensiometer (Zwicki-line)
+ customized 2D-holder

Elastic + Viscoelastic material properties:

- Pre-conditioning
- Stress-relaxation
- Stress-strain curve
Comparing CXL efficacies

- Oxygen availability determines the speed of CXL: short-term irradiation is less effective.
- Irradiate for a long time (with a low UV-irradiance) to reach the maximal stiffening effect.
Linear relationship: CXL-density determines the amount of corneal stiffening.

Best range for CXL:
• significant stiffening
• no adverse effects

REF. Kling S. in press at JRS
Adaptation of the CXL protocol for thin corneas

**AIM:** Inducing a similar density of cross-links like in thicker corneas.

\[
\frac{\text{number of cross-links}}{\text{corneal volume}} = 0.3 - 0.6 \text{ mol/m}^3
\]

**UV fluence at the endothelium** \(\leq 0.3 \text{ J/cm}^2\)
Patient-specific parameter selection
Demarcation line as a function of corneal thickness

- linear correlation relationship
Conclusions

• We have developed a theoretical model that predicts well the CXL efficacy for different corneal thicknesses.

• The density of theoretically induced cross-links is linearly related to the experimental increase in corneal stiffness.

• The model allows a patient-specific adaptation of treatment parameters and allows CXL treatment even in thicknesses <400 μm.
Thank you for your attention