Basics of cross-linking

Fluence, illumination, beam profile

Eberhard Spoerl

University Eye Hospital Dresden

(Direktor: Prof. Dr. med. Lutz E. Pillunat)

Definitions

- Irradiance: E=power/area [mW/cm²]

  (light intensity)

  Light power per area

  example: 3 mW/cm² to 30 mW/cm²

- Irradiation dose: H=E*t [J/cm²]

  (light fluence) t=irradiation time

  light energy per unit area

  example: 5.4J/cm² to 10J/cm²

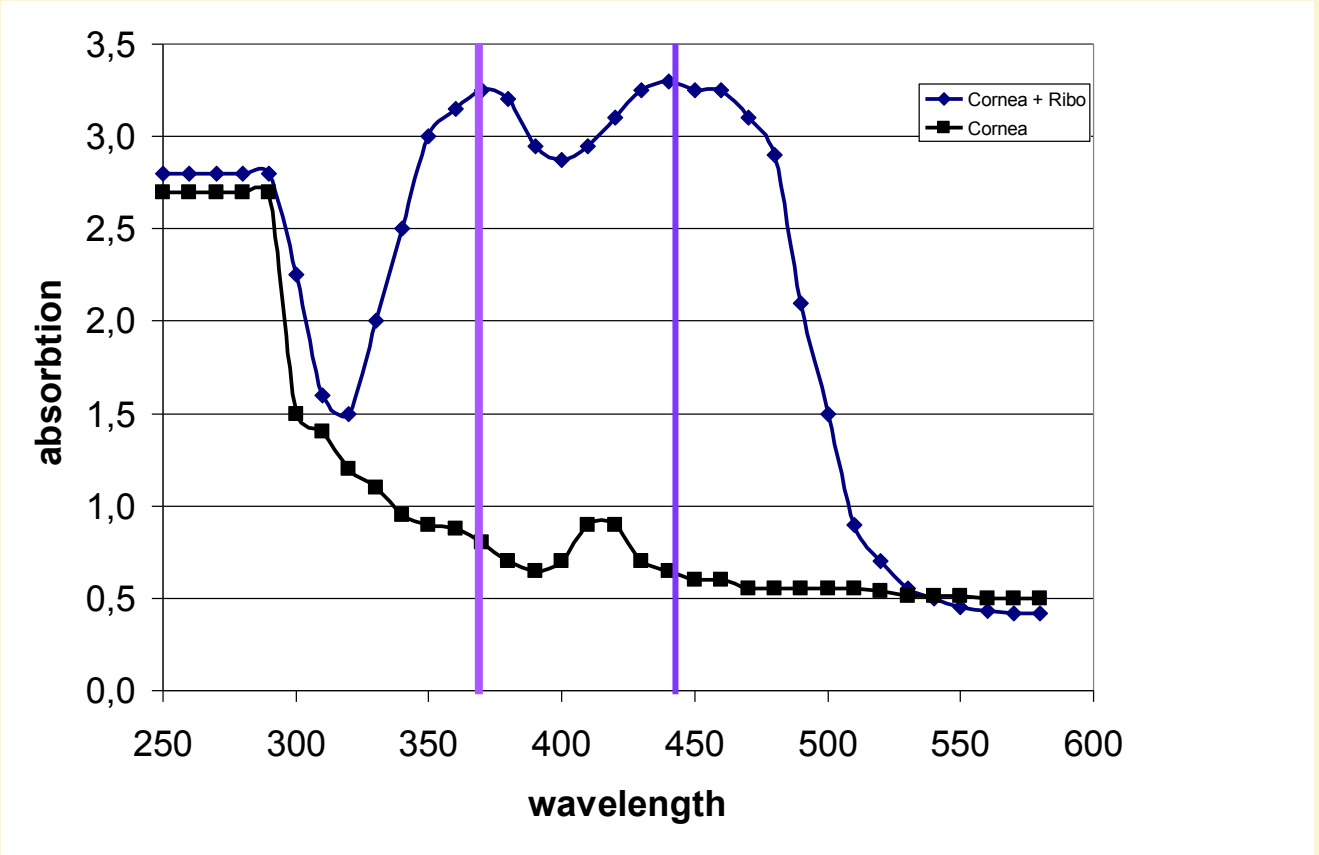
- Continuous irradiation

- Pulsed irradiation:

  example: 1s on/1s off; 10s on 10s off

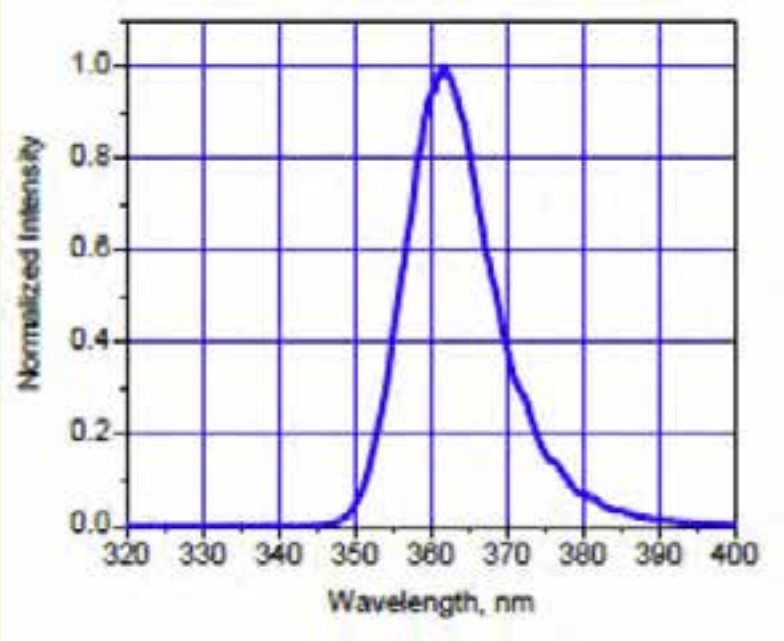
Absorption spectrum of Riboflavin (Vitamin B2)

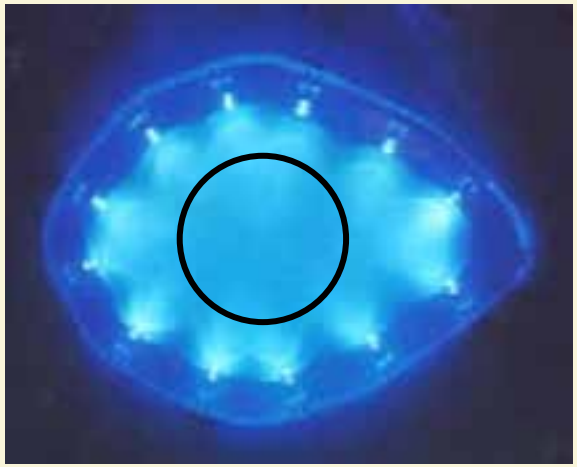
366 nm 445 nm



According to the absorption peak the wavelength was choosen to 365-370 nm

Light-Emitting Diodes with 370 nm



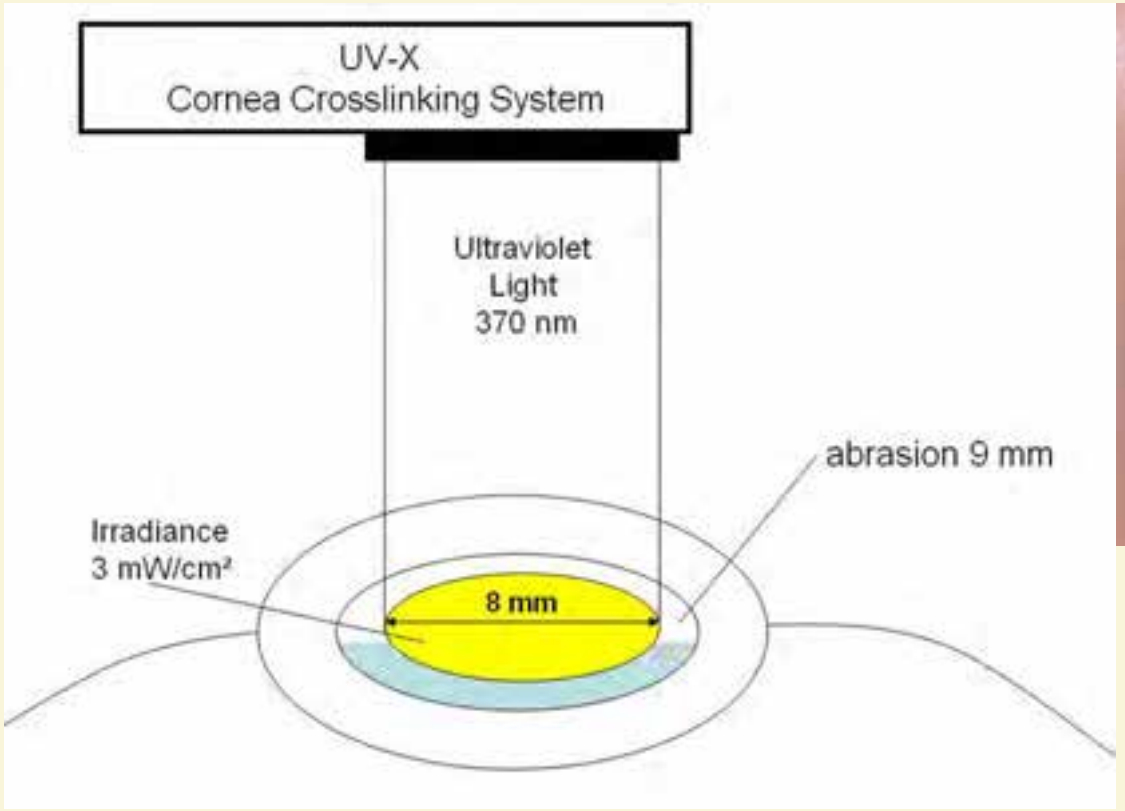


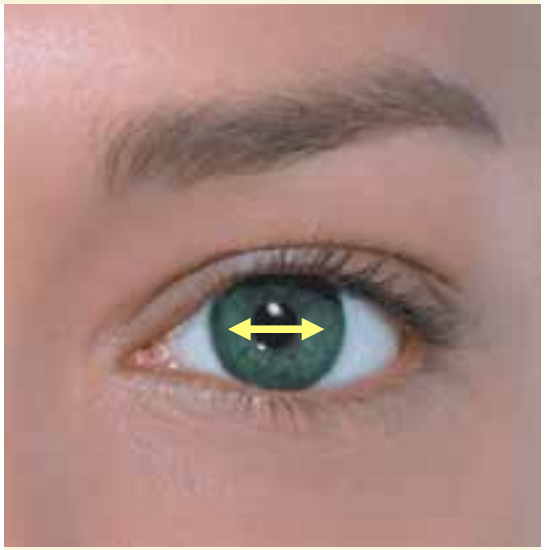
Homogeneous illumination

A clinically used light source must guarantee a perfect homogeneity of the irradiance.

Hot spots may cause localized endothelium cell damage, especially in thin corneas.

Limited area of irradiation





- Only the cornea is irradiated, sclera and limbus are not treated.
- Due to the fluorescence the irradiated area is visible.

Irradiation of Limbus?

safe	damage
rabbit limbal epithelial cells	human limbal epithelial cells
double-standard fluence 10.8 J/cm²	reduced cell expansion
no changed regenerative capacity	reduced regenerative capacity
eccentric CXL may be performed safely in PMD	induced apoptosis,
Richoz O et a. The effect of standard and high-fluence CXL on cornea and limbus. IOVS 2014;55:5783-7	*Thorsrud A et al. CXL in vitro: inhibited regeneration of human limbal epithelial cells after riboflavin-ultraviolet-A-exposure. J Cataract Refract Surg 2012;38:1072-6*

Avoid riboflavin+UVA irradiation on the limbus during CXL.

Irradiation and distance

- Important is the fluence at the corneal surface.
- Adjust the recommended distance

Accelerated CXL

- Accelerated CXL = shorter treatment time (no information about irradiance)
- Increase UVA intensity and reduce irradiation time while maintaining the total amount of fluence (5.4 J/cm^2)
- Optimize the beam profile according to the corneal thickness distribution

Different types of CXL treatments regarding the irradiation devices

Aim: reduced time and increased efficecy

Low fluence <5.4J/cm² standard fluence 5.4 J/cm² high fluence >5.4 J/cm²

low fluence

3.2J/cm² - 5.4J/cm²

thin corneas

Standard CXL

3 mW/cm² 30 min

fluence 5.4 J/cm²

high fluence

7.2J/cm² - 10J/cm²

customized CXL

High intensity accelerated CXL

(same fluence of 5.4 J/cm²)

Bunsen-Roscoe reciprocity law

9 mW/cm² 10 min;

18 mW/cm² 5 min

30 mW/cm² 3 min

Pulsed accelerated CXL

30mW/cm² 6 min

Fluence 5.4J/cm²

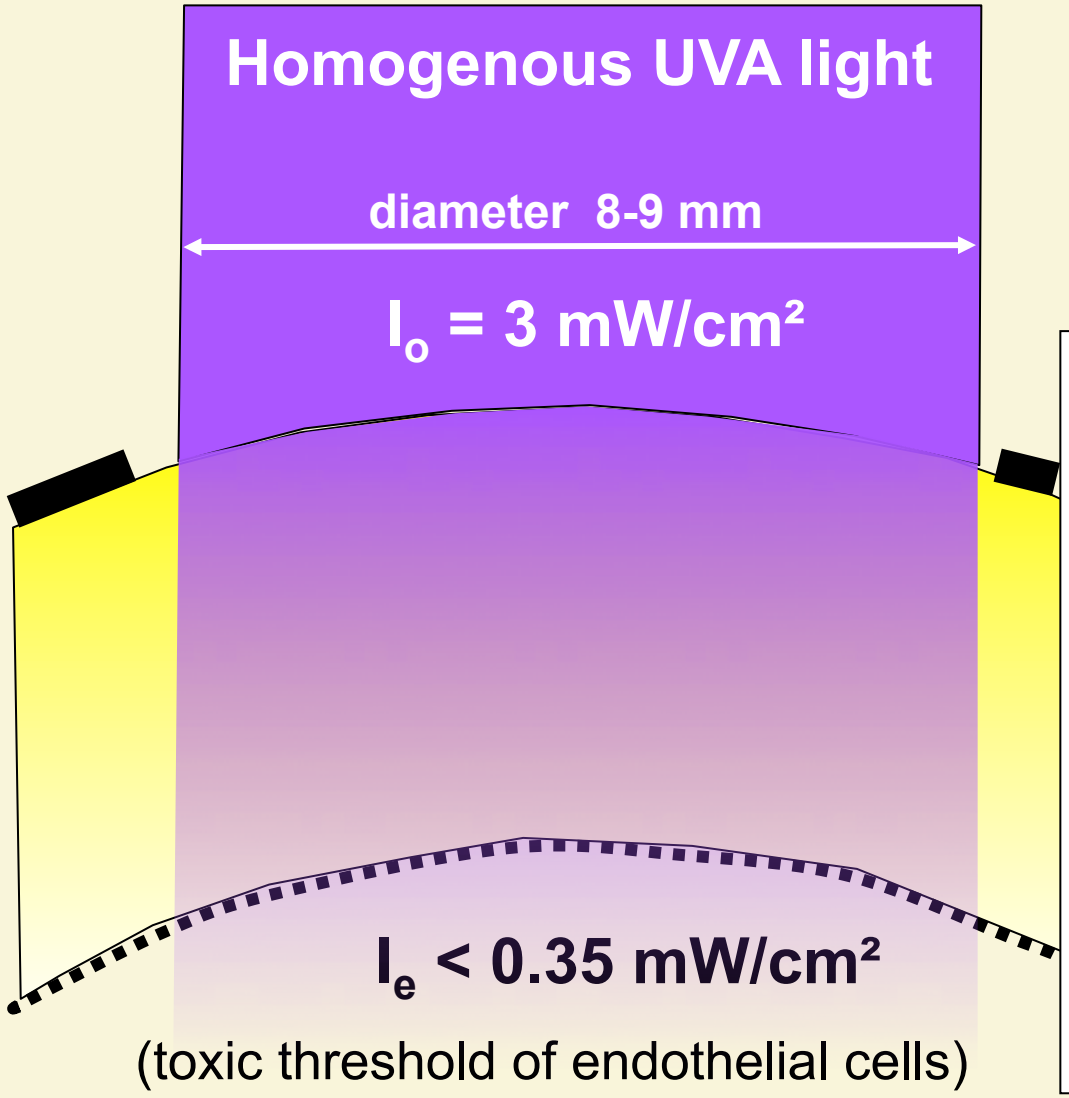
Pulsed accelerated CXL

with high fluence

30mW/cm² 8 min

Fluence 7.2J/cm²

Safety aspects



High absorption

Removal of epithelium

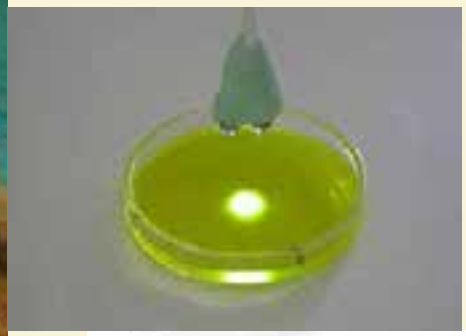
High concentration of riboflavin in stroma (0.1% and 20 min)

Thickness of stroma >400 µm

UV-X (IROC)

KERA-X (Peschke)

PRIA VISION



CBM Vega X-Link
Italy

CL-UVR
India

УФАЛИНК
РОССИА

KXL-accelerated

Devices with higher irradiance

(second generation of cross-linking devices)

5 mW/cm²
Kera-X
Brasil

30 mW/cm²
KXL (Avedro)
USA

18 mW/cm²
CCL-365 (Peschke)
Switzerland

18 mW/cm²
Apollon
Turkey

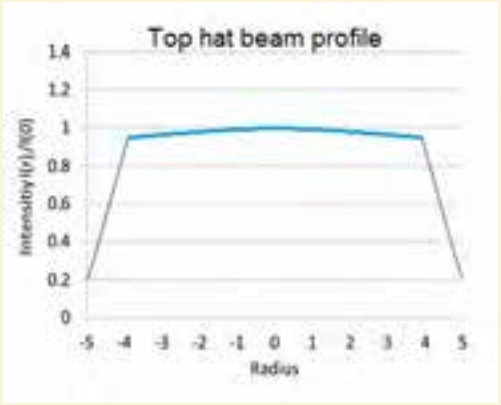
9 mW/cm² 10 min
UV-X (IROC)
Avedro (USA)

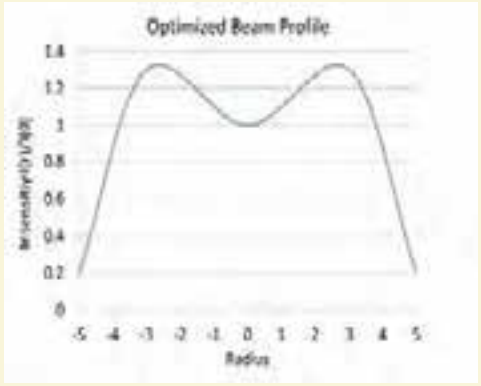
10 mW/cm² 9 min
CBM Vega
Italien

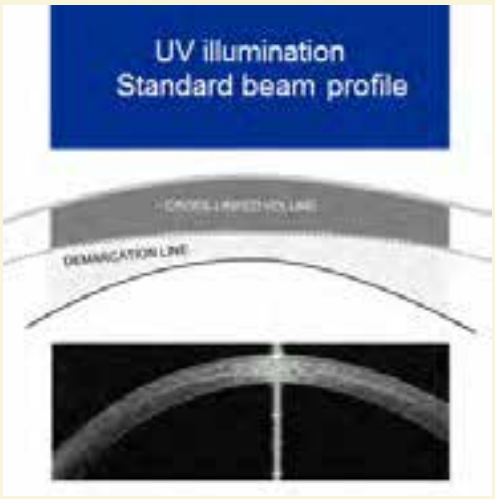
CX-100 China

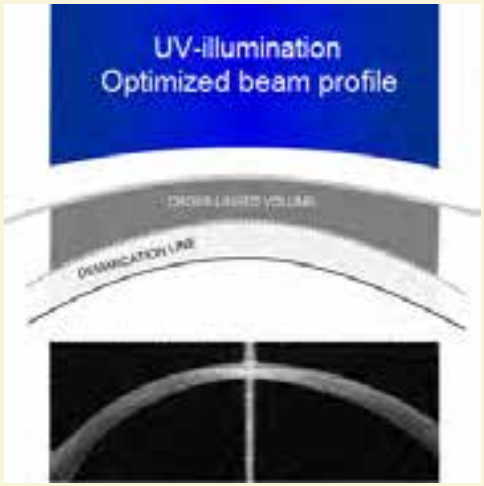
Beam profile

Higher energy in the periphery for deeper corneal stromal penetration - higher efficacy? same treatment: time 10 min









Different demarcation lines but same clinical effect (Herber, 2015)

Mrochen et al. 2014

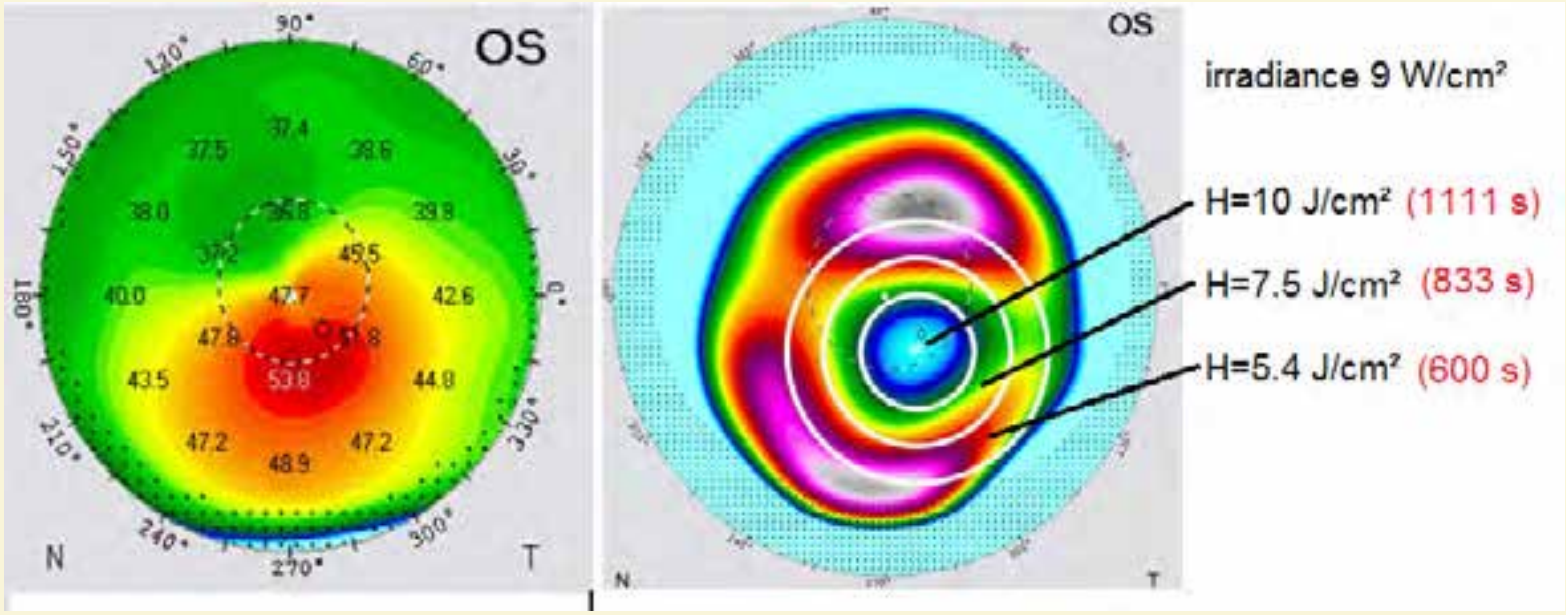
Whole beam profile or customized beam profile

keratoconus	
Local change of the cornea	Change of the whole cornea
local epithelium changes	Thinning of peripherial lamellae
thinnest point	Corneal thickness is also thinner in periphery
Breaks in Bowman membrane	Genetic component
local biomechanical changes	

Customized beam (fluence-time) profile

Profile consist of concentric superposition of 3 circular areas

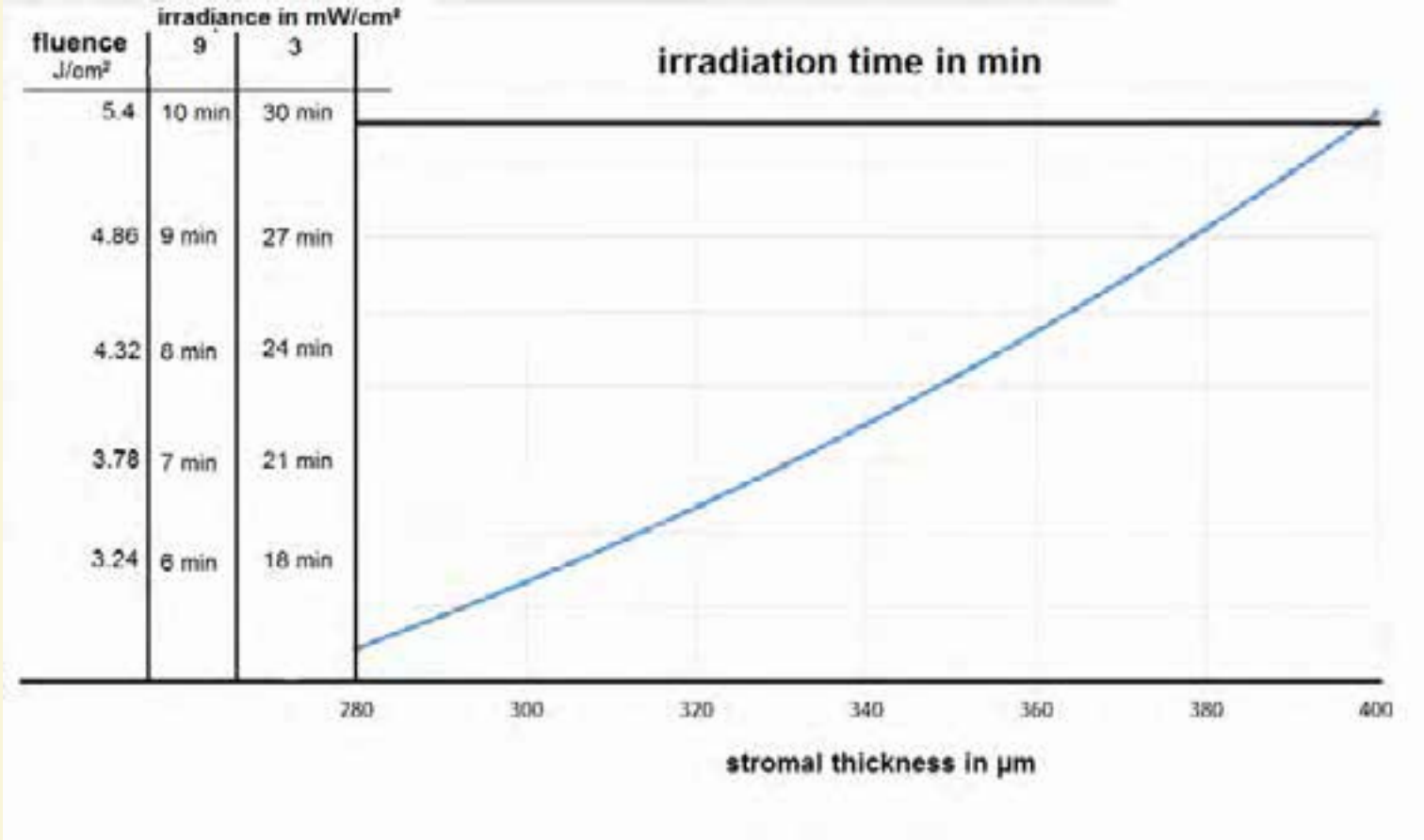
Only the apex is irradiated.



Seiler TG, Fischinger I, Koller T, Zapp D, Frueh BE, Seiler T.
Customized corneal cross-linking one year results. Am J Ophthalmol. 2016;166:14-21

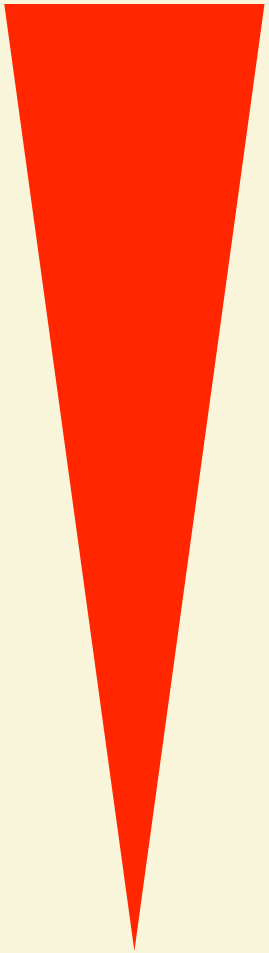
Customized fluence

For thin corneas the fluence can be reduced according the stromal thickness.



Crosslinking effect

- pulsed high intensity CXL
  (7.2J/cm²; 30mW/cm²; 8 min; 10s/10s)
- high intensity CXL
  (7.2J/cm²; 30mW/cm²; 4 min)
- standard CXL
  (5.4J/cm²; 3mW/cm²; 30 min)
- high intensity CXL
  (5.4J/cm²; 30mW/cm²; 3 min)

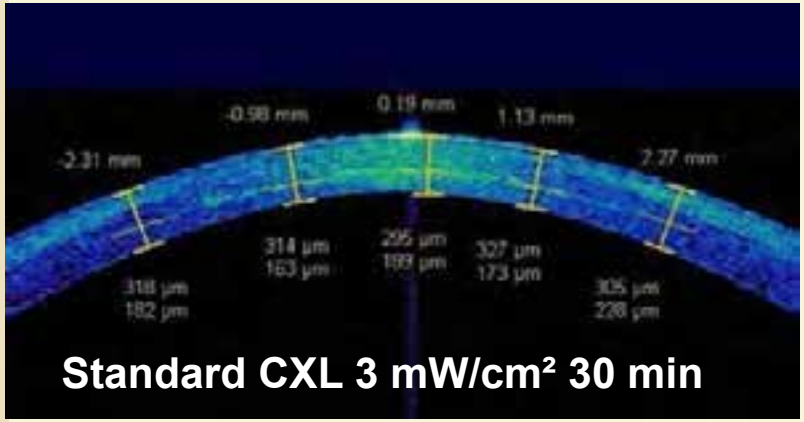


Aldahlawi NH. Enzymatic resistance of corneas crosslinked using riboflavin in conjunction with low energy, high energy, and pulsed UVA irradiation modes. IOVS 2016;57:1547-52

Demarcation line

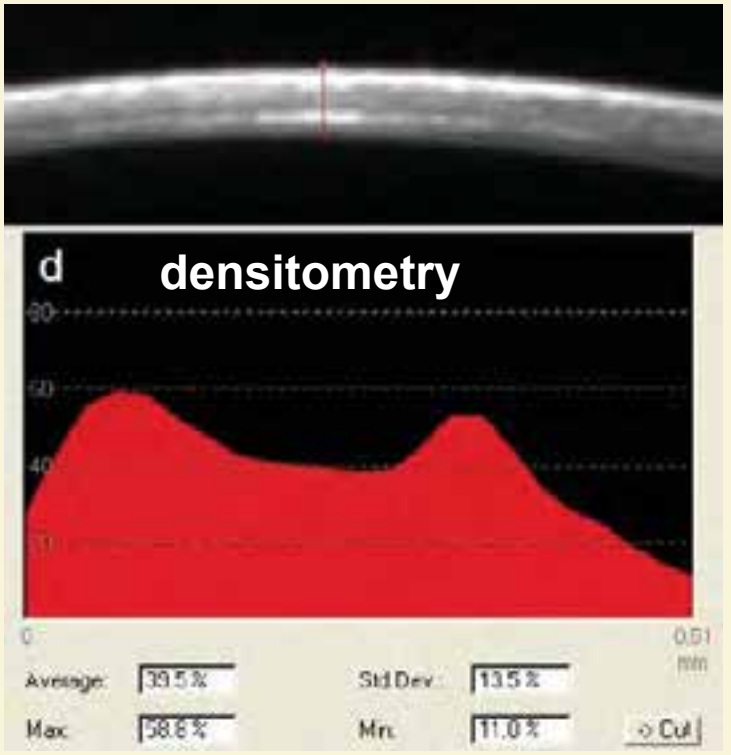
Demarcation line represents the transition zone between acellular (treated) and cellular (untrreated) corneal stroma.

It is a tool for assessment of extent of CXL (not proven, only postulated)



Standard CXL 3 mW/cm² 30 min

Accelerated CXL 9 mW/cm² 10 min



Wittig-Silva *J Refract Surg.* 2013;29(6):410-416

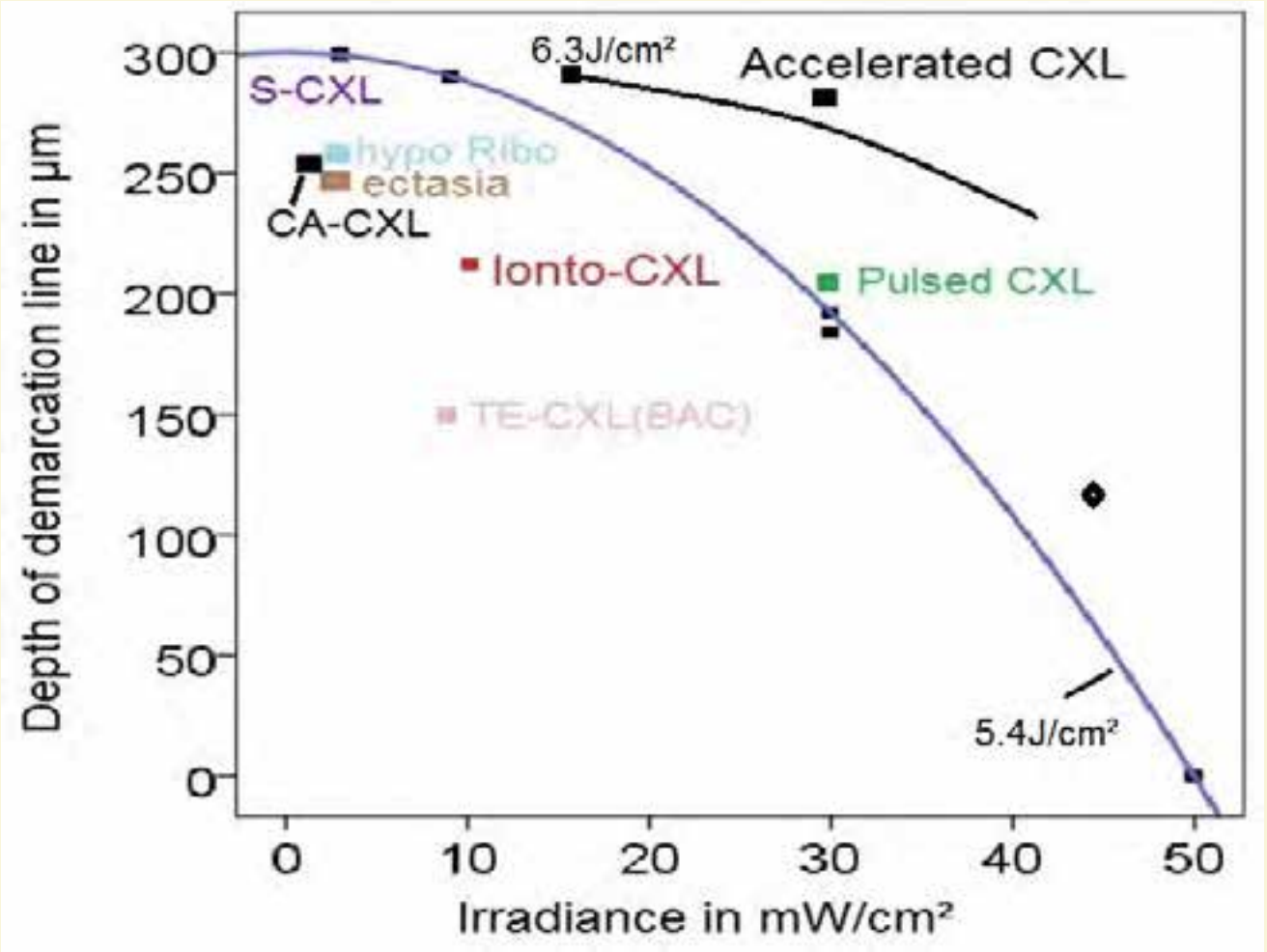
Depth of demarcation line

	Depth in µm	irradiance	time
Standard CXL	350.8±49.3 294.2±51.2	3 mW/cm²	30 min
Hyposomolar Riboflavin	262.9±45.6	3 mW/cm²	30 min
Accelerated CXL	288.5±42.4 160 (150-180)	9 mW/cm² 30 mW/cm²	10 min 4 min
Pulsed CXL	200 (190-215)	30 mW/cm²	8 min
Transepithelial CXL (BAC)	150	3 mW/cm²	30 min
Iontophoresis CXL(without compensation)	212±36	10mW/cm²	9 min

Yam. J. Corneal Collagen Cross-linking Demarcation Line Depth Assessed by Visante OCT After CXL for Keratoconus and Corneal Ectasia. *J Refract Surg*. 2012;28(7):475-481.

Kymionis. Corneal stroma demarcation line after standard and high-intensity collagen cross-linking determined with anterior segment optical coherence tomography. JCRS 2014;40:736–40

Depth of demarcation line for several CXL techniques



demarcation depth= 300-0.12x(irradiance)²

Standard deviation =40µm

Summary

- Determine the irradiation,

  the irradiation time,

  adjust the recommended distance
- Do not irradiate the limbus
- The depth of the demarcation line

  as a measure of the CXL effect

  depends on the irradiation time.

UV-X (IROC)

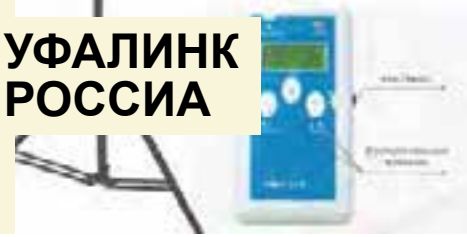
CBM Vega X-Link
Italy

Many thanks for your attention

CX-100 (pen)

CX-100 China

CL-UVR
India



УФАЛИНК
РОССИА

KXL-accelerated

(Avedro, USA)