International
CXL
Experts' Meeting
November 29 – December 1, 2018
Mövenpick Hotel – Zurich Airport

www.cxlexpertsmeeting.com
Advancing cross-linking technology and its clinical application
Letter from the Head of the Scientific Committee

Dear Delegates, Faculty, and Industry Partners,

On behalf of the scientific and organizing committees, I am delighted to welcome you to this year’s CXL Experts’ Meeting in the beautiful city of Zurich. Last year has seen the cross-linking field take some great steps forward – from the possibility of cross-linking of thin corneas, exciting data on the use of PACK-CXL for the treatment of corneal infections, building more momentum to eventually use CXL to correct refractive error and perhaps, coming closer to an epi-off solution. For many of these applications for cross-linking, the finish line might start to be in sight, but we’re not there yet. Nevertheless, this year’s meeting will bring you the latest data from the cross-linking field.

Of course, the CXL Experts’ Meeting is not just about presentations. There are many workshops and wet labs that cover everything from the basics of performing CXL and PACK-CXL for veterinary use, accelerated CXL protocols, keratoconus patient screening and management, to getting the best-possible outcomes when treating keratoconic eyes with CXL and an excimer laser.

This year, the committees have also included a delightful social program: in addition to the interactive coffee breaks, wine and cheese poster sessions and catered lunch breaks, a sit-down banquet dinner on Friday and a Swiss fondue evening on Saturday both provide a great opportunity to meet your peers in a more social context and enjoy Swiss cuisine at its best. I hope to see many of you there.

Finally, I would like to thank you and the faculty for making this meeting possible. Progress isn’t progress if it’s made in a vacuum: the learning you gain at this meeting represents an important dissemination of knowledge. All of us on the scientific and organizing committees hope that you find the meeting interesting, informative, and inspiring, and that you’ll be able to share what you’ve learned with your colleagues. After all, this is knowledge that should improve the lives of many of your patients. Spread the word!

Farhad Hafezi, MD PhD
Head of Scientific Committee, CXL Experts Meeting 2018
Scientific Committee

Farhad Hafezi, MD, PhD
ELZA / University of Geneva / USC Roski Eye Institute, Los Angeles

Theo Seiler, MD, PhD
IROC, Zurich, Switzerland

Paolo Vinciguerra, MD
Humanitas University, Rozzano, Milan, Italy

J. Bradley Randleman, MD
USC Roski Eye Institute, Los Angeles, USA

Rohit Shetty, MD, PhD
Narayana Nethralaya Eye Foundation, Bangalore, India
Meeting Faculty

Renato Ambrosio
Federal University of São Paulo, Rio De Janeiro, Brazil

Adel Barbara
IVISION Refractive Surgery Centre, Haifa, Israel

Michael Belin
University of Arizona, Tucson, AZ, USA

Shihao Chen
Wenzhou Medical College, Wenzhou, China

Efkan Coskunseven
Dunyagogz Group, Istanbul, Turkey

Mouhcine El Bakkali
Clinic of Flap Vision; Rabat University, Morocco

Frank Famose
Acacias Veterinary Clinic, Blagnac, Toulouse, France

Osama Ibrahim
University of Alexandria, Egypt

Sabine Kling
ETH Zurich, Switzerland

Boris Knyazer
Ben-Gurion University of The Negev, Beersheba, Israel

Carina Koppen
University of Antwerp, Belgium

John Marshall
University College London, London, UK

Cosimo Mazzotta
University of Siena, Italy

Jes Mortensen
University of Jönköping, Sweden

David O’Brart
St. Thomas Hospital, London, UK

Simon Pot
Vetsuisse Faculty, University of Zurich, Switzerland

Frederik Raisskup
University Eye Clinic Dresden, Germany

Mohamed Shafik
University of Alexandria, Egypt

Mazen Sinjab
Damascus University, Syria

Emilio Torres
University of Zürich, Switzerland

Riccardo Vinciguerra
St Paul’s Eye Unit and Liverpool University, UK
Thursday, November 29, 2018

Workshops & Wetlabs

08:00 – 10:00  Light for Sight WetLab: “CXL for Beginners”. Room: Zurich I

This wetlab will give concise recommendations and guidelines to treat corneal ectasia of various origins. Hands-on course using CXL irradiation devices and porcine corneas. Specifically, accelerated and transepithelial protocols will be discussed including the use of iontophoresis.

Chairs:
Frederik Raiskup  Farhad Hafezi

08:00 – 10:00  Wetlab: “PACK-CXL (for Veterinarians)”. Room: Zurich II

This workshop will cover the current state of the art in using PACK-Cross-Linking for infectious and non-infectious melting in both human and veterinary applications. Specifically, the use of PACK-CXL in therapy-resistant cases and as an add-on procedure to conventional antimicrobial therapy will be discussed.

Chairs:
Simon Pot  Frank Famose  Boris Knyazer  Jes Mortensen

11:00 – 13:00  SCHWIND eye-tech solutions Workshop: “Treatment strategies using AMARIS excimer laser and CXL in eyes with keratoconus”. Room: Zurich II

This workshop will give an introduction into different therapeutic strategies – i.e. wavefront-guided as well as PTK ablation possibilities with AMARIS excimer laser – for the treatment of keratoconus, and how to combine it with a CXL procedure. Concrete cases will be presented, discussed and ablation profiles developed jointly with the participants. This workshop will give a concise overview about combining tomography and biomechanical measurements using Scheimpflug technology. Actual demonstrations and hands-on devices included. No specific experience required.

Chairs:
Rohit Shetty  Shady Awwad  Farhad Hafezi  Tobias Ewering
14:00 - 16:00  SERVImed Wetlab: "Custom Fast CXL". Room: Zurich I

Moderated by Leopoldo Spadea, Associate Professor and Director of the Ophthalmology Clinic at Policlinico Umberto I – Sapienza University of Rome, this wetlab will give participants the opportunity to acquire basic knowledge of Custom Fast CXL technique and to test it themselves. Every step of the procedure will be discussed in detail, including explanations and background knowledge.

Chair:

Leopoldo Spadea

14:00 - 15:30  Light for Sight Workshop: "Identifying, accessing and managing high risk patients with keratoconus". Room: Zurich II

This workshop will focus on patients with reduced to missing compliance and how to detect and treat progressive keratoconus in these cases, i.e. in patients with Down Syndrome. Concise recommendations for diagnosis and treatment will be given.

Chairs:

J. Bradley Randleman  Emilio Torres  Farhad Hafezi  Nikki Hafezi

16:00 - 18:00  Oculus Workshop "Screening for early ectatic diseases and keratoconus progression". Room: Zurich II

This workshop will give a concise overview about combining tomography and biomechanical measurements using Scheimpflug technology. Actual demonstrations and hands-on devices included. No specific experience required. The presentations are as follows:

Bernardo Lopes: Enhanced Ectasia Diagnosis using Scheimpflug Imaging: Pentacam® + Corvis® ST
Farhad Hafezi: Hormonal Influences on Corneal Topography in Refractive Surgery Candidates and the K-Map Global Prevalence of Keratoconus Study
Riccardo Vinciguerra: Corneal Cross-linking and Biomechanics
Michael Belin: Derivation and Clinical Applications of the Belin ABCD Keratoconus Progression Display

Chairs:

Bernardo Lopes  Farhad Hafezi  Riccardo Vinciguerra  Michael Belin
## Current State: CXL Course

### Basics
**Chairs:** Carina Koppen / Michael Belin

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker (Country)</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Fluence and corneal thickness</td>
<td>Frederik Raiskup (Germany)</td>
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<tr>
<td>09:15</td>
<td>CXL: riboflavin, oxygen, light</td>
<td>Sabine Kling (Switzerland)</td>
</tr>
<tr>
<td>09:30</td>
<td>Corneal structure and biomechanics</td>
<td>John Marshall (UK)</td>
</tr>
<tr>
<td>09:45</td>
<td>Corneal biomechanics: modulating factors</td>
<td>Farhad Hafezi (Switzerland)</td>
</tr>
<tr>
<td>10:00</td>
<td>Role of hydration</td>
<td>Theo G. Seiler (Switzerland)</td>
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<tr>
<td>10:15</td>
<td>Riboflavin absorption kinetics, enzymatic resistance</td>
<td>David O’Brart (UK)</td>
</tr>
<tr>
<td>10:30</td>
<td>Coffee Break</td>
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<tr>
<td>11:00</td>
<td>Corneal Tomography</td>
<td>Michael Belin (USA)</td>
</tr>
<tr>
<td>11:15</td>
<td>Connecting cell, mathematics &amp; biomechanics in CXL outcomes</td>
<td>Rohit Shetty (India)</td>
</tr>
<tr>
<td>11:30</td>
<td>CorVis to measure biomechanics <em>in vivo</em></td>
<td>Riccardo Vinciguerra (Italy)</td>
</tr>
<tr>
<td>11:45</td>
<td>Brillouin microscopy to measure corneal biomechanics</td>
<td>J. Bradley Randleman (USA)</td>
</tr>
<tr>
<td>12:00</td>
<td>Coffee Break</td>
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<tr>
<td>12:00</td>
<td>Panel discussion, questions from audience</td>
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### CXL Protocols for Keratoconus
**Chairs:** Adel Barbara / Mohammed Shafik

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker (Country)</th>
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<tbody>
<tr>
<td>13:30</td>
<td>Epi-off “Dresden”</td>
<td>Frederik Raiskup (Germany)</td>
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<tr>
<td>13:40</td>
<td>Epi-off accelerated</td>
<td>Farhad Hafezi (Switzerland)</td>
</tr>
<tr>
<td>13:50</td>
<td>Epi-on</td>
<td>Theo Seiler (Switzerland)</td>
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<tr>
<td>14:00</td>
<td>Pulsed</td>
<td>Cosimo Mazzotta (Italy)</td>
</tr>
<tr>
<td>14:10</td>
<td>Iontophoresis</td>
<td>Paolo Vinciguerra (Italy)</td>
</tr>
<tr>
<td>14:20</td>
<td>Which protocol to use when?</td>
<td>Panel &amp; Audience</td>
</tr>
<tr>
<td>14:50</td>
<td>Coffee Break</td>
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### CXL as a Refractive Procedure

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker (Country)</th>
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<tbody>
<tr>
<td>15:30</td>
<td>Current state</td>
<td>Theo Seiler (Switzerland)</td>
</tr>
<tr>
<td>15:45</td>
<td>Discussion</td>
<td>(Seiler, Randleman, Ibrahim, Hafezi, P. Vinciguerra, Shetty, Coskunseven, Frucht-Pery, O’Brart) &amp; all</td>
</tr>
</tbody>
</table>

### LASIK Xtra / PRK Xtra

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<th>Time</th>
<th>Topic</th>
<th>Speaker (Country)</th>
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</thead>
<tbody>
<tr>
<td>16:00</td>
<td>Current state</td>
<td>Raj Rajpal (USA)</td>
</tr>
<tr>
<td>16:15</td>
<td>Discussion</td>
<td>(Chen, Randleman, Shetty, Raiskup, Belin, Shafik) &amp; all</td>
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</tbody>
</table>

### PACK-CXL

<table>
<thead>
<tr>
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<th>Topic</th>
<th>Speaker (Country)</th>
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</thead>
<tbody>
<tr>
<td>16:30</td>
<td>Current state</td>
<td>Emilio Torres (Switzerland)</td>
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</table>

### Customized CXL

<table>
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<th>Topic</th>
<th>Speaker (Country)</th>
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</thead>
<tbody>
<tr>
<td>16:45</td>
<td>Current state</td>
<td>Theo G. Seiler (Switzerland)</td>
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</tbody>
</table>

### Therapeutic CXL & PRK

<table>
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<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker (Country)</th>
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<tbody>
<tr>
<td>16:45</td>
<td>Current state</td>
<td>Mohammed Shafik (Egypt)</td>
</tr>
<tr>
<td>17:00</td>
<td>Discussion</td>
<td>(Shafik, Sinjab, Shetty, Ibrahim, Chen, Coskunseven, Mazzotta) &amp; all</td>
</tr>
<tr>
<td>17:15</td>
<td>End of CXL Course</td>
<td></td>
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### Social events

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Details</th>
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<tbody>
<tr>
<td>17:45</td>
<td>Poster Session / Wine &amp; Cheese – everyone welcome</td>
<td></td>
</tr>
<tr>
<td>19:30</td>
<td>Congress Banquet Dinner (reservations required)</td>
<td></td>
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</table>
## Saturday, November 31, 2018

### The Future: Scientific Program

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>08:25</td>
<td><strong>Introduction and Welcome</strong></td>
<td>Farhad Hafezi (Switzerland)</td>
</tr>
<tr>
<td><strong>Basics</strong>&lt;br&gt;Chairs: John Marshall / Rohit Shetty</td>
<td><strong>Presenting Author</strong></td>
<td></td>
</tr>
<tr>
<td>08:30</td>
<td>Effects of drug formulation, supplemental oxygen, and UV delivery on epi-on CXL</td>
<td>Grace Lytle</td>
</tr>
<tr>
<td>08:38</td>
<td>Novel chemical cross-linker for the cornea to treat keratoconus</td>
<td>Vito Romano</td>
</tr>
<tr>
<td>08:46</td>
<td>Brillouin microscopy of human corneas before and after epi-on cross-linking</td>
<td>Doyle Stulting</td>
</tr>
<tr>
<td>08:54</td>
<td>Femtosecond laser induced corneal cross-linking towards correction of refractive errors – a parametric study</td>
<td>Sinisa Vukelic</td>
</tr>
<tr>
<td>09:02</td>
<td><strong>Q&amp;A session</strong></td>
<td></td>
</tr>
<tr>
<td>09:10</td>
<td>Translational impact of lysyl oxidase (LOX) on cross-linking/refractive surgery and allied novel point-of-care diagnostic kit</td>
<td>Pooja Khamar</td>
</tr>
<tr>
<td>09:18</td>
<td>Impact of stromal oxygen dynamics on high-irradiance epi-on cross-linking</td>
<td>Desmond Adler</td>
</tr>
<tr>
<td>09:26</td>
<td>Ocular surface immune trafficking and eye rubbing in keratoconus, and its impact on treatment outcomes</td>
<td>Pavitra Patel</td>
</tr>
<tr>
<td>09:34</td>
<td>Corneal UV-light cross-linking promotes high-risk corneal graft survival by regressing mature corneal lymphatic and blood vessels</td>
<td>Yanhong Hou</td>
</tr>
<tr>
<td>09:42</td>
<td><strong>Q&amp;A session</strong></td>
<td></td>
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<tr>
<td>09:50</td>
<td>Safety of high-dose, transepithelial, accelerated CXL with supplemental oxygen on human and monkey eyes</td>
<td>Alexandra Nicklin</td>
</tr>
<tr>
<td>09:58</td>
<td><em>In vivo</em> study of femtosecond laser cross-linking of corneal tissue to correct refractive errors</td>
<td>Sinisa Vukelic</td>
</tr>
<tr>
<td>10:06</td>
<td>Cross-linking of Kpro corneal carrier donor tissue to prevent keratolysis</td>
<td>Joseph Ciolino</td>
</tr>
<tr>
<td>10:14</td>
<td><strong>Q&amp;A session</strong></td>
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<tr>
<td>10:20</td>
<td><strong>Coffee Break</strong></td>
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</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Title</td>
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<tr>
<td>10:50</td>
<td>PACK-CXL</td>
<td>Visual outcomes and graft survival rates of optical corneal transplants after Rose Bengal Photodynamic Antimicrobial Therapy as adjunctive treatment for infectious keratitis</td>
</tr>
<tr>
<td>10:58</td>
<td>PACK-CXL</td>
<td>In-vivo and ex-vivo assessment of corneal endothelium and limbal stem cell niche following Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT)</td>
</tr>
<tr>
<td>11:06</td>
<td>PACK-CXL</td>
<td>PACK-CXL as adjuvant treatment for acanthamoeba keratitis: a case study</td>
</tr>
<tr>
<td>11:14</td>
<td>Q&amp;A Session</td>
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<tr>
<td>11:30</td>
<td>CXL Plus I</td>
<td>An in situ UV polymerised artificial cornea for custom SMILE surgery</td>
</tr>
<tr>
<td>11:38</td>
<td>CXL Plus I</td>
<td>Topo-guided Removal of Epithelium in Keratoconus (TREK) and accelerated cross-linking – novel tissue sparing customised treatment of keratoconic eyes</td>
</tr>
<tr>
<td>11:46</td>
<td>CXL Plus I</td>
<td>Photorefractive keratectomy in patients with primary keratoconus after corneal cross-linking</td>
</tr>
<tr>
<td>11:54</td>
<td>CXL Plus I</td>
<td>Combined epithelium-off topography-guided photorefractive keratomecy and corneal cross-linking</td>
</tr>
<tr>
<td>12:02</td>
<td>Q&amp;A session</td>
<td></td>
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<tr>
<td>12:15</td>
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<tr>
<td>13:30</td>
<td>CXL Plus II</td>
<td>A novel method to study Bowman’s Layer Topography – a paradigm shift in understanding the corneal surface</td>
</tr>
<tr>
<td>13:38</td>
<td>CXL Plus II</td>
<td>Combined SMILE and CXL for moderate to high myopia in patients with thin or steep corneas</td>
</tr>
<tr>
<td>13:46</td>
<td>CXL Plus II</td>
<td>Complications of combined CXL and PRK</td>
</tr>
<tr>
<td>13:54</td>
<td>CXL Plus II</td>
<td>Case report: allograft lenticule onlay implantation with PTK after CXL in KC treatment</td>
</tr>
<tr>
<td>14:02</td>
<td>Q&amp;A session</td>
<td></td>
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<tr>
<td>14:10</td>
<td>CXL for Keratoconus I</td>
<td>The independent effect of various treatment modalities on cross-linking effectiveness studied in 670 eyes</td>
</tr>
<tr>
<td>Time</td>
<td>Presentation Title</td>
<td>Presenter</td>
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<tr>
<td>14:18</td>
<td>Accelerated versus conventional corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials</td>
<td>Hidenaga Kobashi</td>
</tr>
<tr>
<td>14:26</td>
<td>Assessment of the association between <em>in-vivo</em> corneal biomechanical changes after collagen cross-linking and depth of demarcation line in patients with progressive keratoconus</td>
<td>Riccardo Vinciguerra</td>
</tr>
<tr>
<td>14:34</td>
<td>Q&amp;A session</td>
<td></td>
</tr>
<tr>
<td>14:42</td>
<td>Is Pellucid Marginal Degeneration a variant of keratoconus or a different entity – structural, molecular and biomechanical changes and its impact on cross-linking</td>
<td>Ritika Dalal</td>
</tr>
<tr>
<td>14:50</td>
<td>Effects of corneal cross-linking on tensile properties of posterior and anterior corneal flaps</td>
<td>Hamed Hatami-Marbini</td>
</tr>
<tr>
<td>14:58</td>
<td>Mega-dose dietary riboflavin and direct sunlight exposure in the treatment of keratoconus and post-refractive surgery ectasia of the cornea – an update</td>
<td>John Jarstad</td>
</tr>
<tr>
<td>15:06</td>
<td>Q&amp;A session</td>
<td></td>
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<tr>
<td>15:15</td>
<td>Congress group photo</td>
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<tr>
<td>15:40</td>
<td>Coffee break</td>
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**CXL for Keratoconus II**  
*Chairs: Shihao Chen / Michael Belin*

<table>
<thead>
<tr>
<th>Time</th>
<th>Presentation Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:10</td>
<td>Customized CXL for keratoconus – 3-year results</td>
<td>Theo G. Seiler</td>
</tr>
<tr>
<td>16:18</td>
<td>Enhanced-Fluence Pulsed-Light Iontophoresis Corneal Cross Linking: 1-year morphological and clinical results</td>
<td>Cosimo Mazzotta</td>
</tr>
<tr>
<td>16:26</td>
<td>Is corneal cross-linking treatment effective in stabilizing the corneal curvature during pregnancy in keratoconus patients?</td>
<td>Ozge Sarac</td>
</tr>
<tr>
<td>16:34</td>
<td>Q&amp;A session</td>
<td></td>
</tr>
<tr>
<td>16:42</td>
<td>Automated detection and classification of corneal haze using optical coherence tomography in keratoconus eyes after cross-linking</td>
<td>Shady Awwad</td>
</tr>
<tr>
<td>16:50</td>
<td>Athens Protocol after femtosecond-assisted intracorneal ring implantation</td>
<td>Bernardo Lopes</td>
</tr>
<tr>
<td>16:58</td>
<td>Corneal cross-linking (CXL) with two different riboflavin solutions: A randomized, controlled trial</td>
<td>Gerald Schmidinger</td>
</tr>
<tr>
<td>17:06</td>
<td>Q&amp;A session</td>
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<tr>
<td>17:15</td>
<td>Awards</td>
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<td>No</td>
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<tr>
<td>1</td>
<td>When corneal cross-linking additionally and dramatically improves the visual acuity, a pleasant surprise!</td>
<td>Rawya Diab</td>
</tr>
<tr>
<td>2</td>
<td>The results of the accelerated corneal cross-linking in initial stages of progressive keratoconus</td>
<td>Liudmyla Troichenko</td>
</tr>
<tr>
<td>3</td>
<td>Corneal thinning and refractive index change monitored by optical coherence tomography and optical path length measurement during UVA-riboflavin corneal cross-linking</td>
<td>Xin Tan</td>
</tr>
<tr>
<td>4</td>
<td>Contact lens assisted cross linking for progressive keratoconus with thin corneas about 47 cases</td>
<td>Yasser Rifay</td>
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<tr>
<td>5</td>
<td>Multiphoton tomography for accelerated cross-linking follow-up</td>
<td>Ana Batista</td>
</tr>
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<td>6</td>
<td>Management of post LASIK ectasia</td>
<td>Maja Bohac</td>
</tr>
<tr>
<td>7</td>
<td>A prospective three-armed study on pain and wound healing after routine epithelium-off cross-linking</td>
<td>Nienke Soeters</td>
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<td>8</td>
<td>A disposable UV-A cross-linking technology for optimized energy transfer to the cornea.</td>
<td>Albert Daxer</td>
</tr>
<tr>
<td>9</td>
<td>Early complications secondary to corneal cross-linking of keratoconus using two different riboflavin solutions</td>
<td>Gerald Schmidinger</td>
</tr>
<tr>
<td>10</td>
<td>Long term results of CXL for corneal ectasia: Egyptian experience over 12 years</td>
<td>Osama Ibrahim</td>
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<tr>
<td>11</td>
<td>Influencing factors on topographic outcome of corneal cross-linking for keratoconus</td>
<td>Denise Wajnsztajn Vamos</td>
</tr>
<tr>
<td>12</td>
<td>How do we calculate the exact pre-operative pachymetry POP during CXL epi OFF?</td>
<td>Mouhcine El Bakkali</td>
</tr>
<tr>
<td>13</td>
<td>Accelerated corneal cross-linking: Faster, higher, but which protocol is biomechanically stronger?</td>
<td>Philip Jaycock</td>
</tr>
</tbody>
</table>

**CXL pre-clinical / translational**

<table>
<thead>
<tr>
<th>No</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Long term effect of corneal cross linking on endothelial cell count in patients with keratoconus</td>
</tr>
<tr>
<td>15</td>
<td>Increased resistance against collagenase digestion of porcine corneas cross-linked by hypo-osmolar and hyper-osmolar formulations of riboflavin/ultra-violet A or WST11/near-infrared light.</td>
</tr>
<tr>
<td>16</td>
<td>Effects of eye motion and active eye tracking on refractive cross-linking</td>
</tr>
<tr>
<td></td>
<td>Title</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>17</td>
<td>Comparison of waveform derived corneal stiffness and stress-strain extensometry derived corneal stiffness using different cross-linking irradiances: A prospective study with air-puff applanation of ex vivo porcine eyes</td>
</tr>
<tr>
<td>18</td>
<td>Alcohol cotton bud technique for removal of corneal epithelium at the slit lamp in corneal cross-linking</td>
</tr>
<tr>
<td>19</td>
<td>Changes in tear biomarkers in keratoconus after accelerated cross-linking</td>
</tr>
<tr>
<td>20</td>
<td>Large field of view corneal epithelium and Bowman's layer thickness maps in keratoconic and healthy eyes</td>
</tr>
<tr>
<td>21</td>
<td>Safety and efficacy of collagen cross linking (CXL) of human corneal transplants ex vivo: a pilot study.</td>
</tr>
<tr>
<td>22</td>
<td>Measuring the force exerted during eye rubbing</td>
</tr>
</tbody>
</table>

**Refractive CXL**

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Author</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>To evaluate the effect of a novel radial corneal inlay implant (Corneal Arches) in the keratoconic eye.</td>
<td>Marwan Ghabra</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

**CXL Plus (Combination procedures)**

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Author</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Sectorial PTK+CXL for keratoconus treatment</td>
<td>Safwan Albayati</td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>25</td>
<td>Concurrent versus sequential treatment with corneal cross-linking and intracorneal ring segments (Intacs) for keratoconus</td>
<td>Steven Greenstein</td>
<td>United States</td>
</tr>
</tbody>
</table>
CXL Experts’ Meeting, Zurich 2018
Abstracts

Table of Contents

CXL For Ectasia

A disposable UV-A cross-linking technology for optimized energy transfer to the cornea. 16
A prospective three-armed study on pain and wound healing after routine epithelium-off cross-linking 17
Accelerated versus conventional corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials 18
Assessment of the association between in vivo corneal biomechanical changes after corneal cross-linking and depth of demarcation line in patients with progressive keratoconus. 19
Automated detection and classification of corneal haze using optical coherence tomography in keratoconus eyes after cross-linking 20
Brillouin microscopy of human corneas before and after epi-on cross-linking 21
Contact lens assisted cross-linking for progressive keratoconus with thin corneas about 47 cases 22
Corneal cross-linking (CXL) with two different riboflavin solutions. A randomized, controlled trial. 23
Corneal thinning and refractive index change monitored by optical coherence tomography and optical path length measurement during UVA-riboflavin corneal cross-linking 24
Customized CXL for keratoconus – 3-year results 25
Early complications secondary to corneal cross-linking of keratoconus using two different riboflavin solutions 26
Effects of corneal cross-linking on tensile properties of posterior and anterior corneal flaps 27
Effects of drug formulation, supplemental oxygen, and UV delivery on epi-on CXL 28
Enhanced-fluence pulsed-light iontophoresis corneal cross-linking: 1-year morphological and clinical results 29
How do we calculate the exact pre-operative pachymetry POP during cross-linking epi-OFF? 30
Impact of stromal oxygen dynamics on high-irradiance epi-on cross-linking 31
Influencing factors on topographic outcome of corneal cross-linking for keratoconus 32
Is corneal cross-linking treatment effective in stabilizing the corneal curvature during pregnancy in keratoconus patients? 33
Is Pellucid Marginal Degeneration a variant of keratoconus or a different entity – structural, molecular and biomechanical changes and its impact on cross-linking 34
Long term results of CXL for corneal ectasia: Egyptian experience over 12 years 35
Management of post-LASIK ectasia 36
Mega-dose dietary riboflavin and direct sunlight exposure in the treatment of keratoconus and post refractive surgery ectasia of the cornea – an update. 37
Multiphoton tomography foraccelerated-cross-linking follow-up 38
Novel chemical cross-linker for the cornea to treat keratoconus 39
The independent effect of various treatment modalities on cross-linking effectiveness studied in 670 eyes 40
The results of the accelerated corneal cross-linking in initial stages of progressive keratoconus 41
Translational impact of lysyl oxidase (LOX) on cross-linking/refractive surgery and allied novel point-of-care diagnostic kit. 42
When corneal cross-linking additionally and dramatically improves the visual acuity, a pleasant surprise! 43

CXL Plus (Combination procedures)

A novel method to study Bowman’s layer topography - A paradigm shift in understanding the corneal surface 46
Athens protocol after femtosecond-assisted intracorneal ring implantation 47
| Case Report: Allograft lenticule onlay implantation with PTK after CXL in KC treatment | 48 |
| Combined epithelium-off topography-guided photorefractive keratotomy and corneal cross-linking | 49 |
| Combined SMILE and CXL for moderate to high myopia in patients with thin or steep corneas | 50 |
| Complications of combined CXL and PRK | 51 |
| Concurrent versus sequential treatment with corneal cross-linking and intracorneal ring segments (Intacs) for keratoconus | 52 |
| Corneal UV-light cross-linking promotes high-risk corneal graft survival by regressing mature corneal lymphatic and blood vessels | 53 |
| Sectorial PTK+CXL for keratoconus treatment | 54 |

**PACK-CXL For Keratitis**

*In vivo and ex vivo* assessment of corneal endothelium and limbal stem cell niche following Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT). | 56 |
PACK-CXL as adjuvant treatment for acanthamoeba keratitis. A case study. | 57 |
Visual outcomes and graft survival rates of optical corneal transplants after Rose Bengal Photodynamic Antimicrobial Therapy as adjunctive treatment for infectious keratitis. | 58 |

**Refractive CXL**

An *in situ* UV polymerised artificial cornea for “custom smile” surgery | 61 |
Effects of eye motion and active eye tracking on refractive cross-linking | 62 |
Femtosecond laser induced corneal cross-linking towards correction of refractive errors – a parametric study | 63 |
Photorefractive keratotomy in patients with primary keratoconus after corneal cross-linking | 64 |
To evaluate the effect of a novel radial corneal inlay implant (Corneal Arches) in the keratoconic eye. | 65 |
Topo-guided Removal of Epithelium in Keratoconus (TREK) and accelerated cross-linking – novel tissue sparing customised treatment of keratoconic eyes | 66 |

**CXL Pre-clinical / Translational**

Alcohol cotton bud technique for removal of corneal epithelium at the slit lamp in corneal cross-linking | 68 |
Changes in tear biomarkers in keratoconus after accelerated cross-linking | 69 |
Comparison of waveform derived corneal stiffness and stress-strain extensometry derived corneal stiffness using different cross-linking irradiances: a prospective study with air-puff applanation of *ex vivo* porcine eyes | 70 |
Cross-linking of Kpro corneal carrier donor tissue to prevent keratolysis | 71 |
*In vivo* study of femtosecond laser cross-linking of corneal tissue to correct refractive errors | 72 |
Increased resistance against collagenase digestion of porcine corneas cross-linked by hypo-osmolar and hyper-osmolar formulations of riboflavin/ultraviolet A or WST11/near-infrared light. | 73 |
Large field of view corneal epithelium and Bowman’s layer thickness maps in keratoconic and healthy eyes | 74 |
Long-term effect of corneal cross-linking on endothelial cell count in patients with keratoconus | 75 |
Measuring the force exerted during eye rubbing | 76 |
Ocular surface immune trafficking and eye rubbing in keratoconus, and its impact on treatment outcomes | 77 |
Safety and efficacy of cross-linking (CXL) of human corneal transplants *ex vivo*: a pilot study. | 78 |
Safety of high-dose, transepithelial, accelerated CXL with supplemental oxygen on human and monkey eyes | 79 |
A disposable UV-A cross-linking technology for optimized energy transfer to the cornea.

Dr. Albert Daxer
1. CISIS Keratoconus Center

Purpose
In conventional corneal cross-linking the UV-A irradiation energy transferred to a certain area of the cornea depends on the local steepness of that area. The higher the local steepness the lower the energy transfer. Unfortunately, the steepest area in a keratoconic cornea is the cone itself. The position of the cone as well as the related steepness varies, however, from case to case. The purpose of this presentation is to propose a new disposable technology which provides a homogeneous UV-A irradiation energy transfer to the cornea independent from the individual corneal shape.

Materials and Methods
The technology uses a battery-driven UV-A light emitting diode (LED) with an opening angle of 80 degree. The UV-A light is emitted into a cylindrical irradiation channel which is mounted on the distal end to a housing which contains the battery and the UV-A LED and on the proximal end to the eye via a suction-ring. The irradiation channel is equipped with a diffusely reflecting inner surface which allows multiple reflections of the UV-A light on its path from the light source to the cornea. The cornea protrudes into the irradiation channel during the treatment.

Results
The replacement of an UV-A light running mainly parallel to the optical axis along a free irradiation-path as used in the conventional cross-linking technology by the disposable irradiation channel and an UV-A light source with an opening angle of some 80 degrees results in a beam profile where the UV-A light strikes the cornea virtually from all directions. Therefore, the energy transfer to the cornea is homogeneous and independent from the individual shape of the cornea.

Conclusion
The homogeneous energy transfer to the cornea as provided by the presented technology may be a further step toward the improvement of the effectivity of cornea cross-linking for keratoconus. The new technology is already approved as a medical device in Europe since December 2017. Further post-market long-term studies are under preparation.
A prospective three-armed study on pain and wound healing after routine epithelium-off cross-linking

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1. University Medical Center Utrecht, 2. University Utrecht

**Purpose**
To investigate the effect of three different regimes on pain and wound healing after corneal cross-linking (CXL).

**Materials and Methods**
This single-centre prospective cohort study included 60 eyes of 60 patients with progressive keratoconus scheduled for accelerated 9mW/mm² epi-off CXL. Patients received a bandage lens (n=20), occlusive patch (n=20) or antibiotic ointment only (n=20) after treatment. Primary outcome measures were postoperative pain and quality of life, as measured by the McGill Pain Questionnaire and Visual Analogue Score (VAS), and epithelial healing at two days. Secondary outcomes were correlations between pain and psychological factors that influence the perception of pain (Depression Anxiety Stress Score & Pain Catastrophizing Score), and the consumption of oral pain medication as prescribed according to the WHO guidelines.

**Results**
On average, patients experienced considerable pain after CXL (mean VAS 5.9 ± 2.6). The postoperative regimen did not significantly affect the amount of experienced pain, though the antibiotic ointment group reported a higher VAS (VAS 6.6 vs. 5.6 & 5.6; P=0.450). Occlusive patching showed a trend to quicker resolution of the epithelial defect (85% completely healed vs. 65% with lenses and 70% with antibiotic ointment; P=0.434). Correlations with potential pain-modulating psychological factors were weak (R²<0.3) and not significant. The actual use of pain medication corresponded poorly to the prescribed use and was not correlated with differences in pain perception. No adverse events occurred.

**Conclusion**
Our study demonstrated a clinical equivalence of the three regimes in combating the postoperative pain experienced after routine CXL. Wound healing appeared quicker in the occlusive patch group. Since contact lenses incur a small risk of keratitis, we argue that the clinical tradition of using bandage contact lenses after CXL should be re-evaluated. Occlusive patching is proposed as the new standard of care.
Accelerated versus conventional corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials

Dr. Hidenaga Kobash‡
1. Keio University

Purpose
To compare the efficacy and safety of accelerated corneal cross-linking (CXL) to conventional Dresden protocol in progressive keratoconus by summarizing randomized controlled trials (RCTs) using a meta-analysis.

Materials and Methods
Cochrane databases and MEDLINE were searched for RCTs. Trials meeting the selection criteria were quality appraised, and the data were extracted by two independent authors. A comprehensive search was performed using the Cochrane Collaboration methodology to evaluate the clinical outcomes of accelerated CXL (18 mW/cm² or more for 5 min or less) and conventional Dresden protocol (3 mW/cm² for 30 min) for treating progressive keratoconus. Estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the outcomes during 12-month observation periods. Postoperative demarcation line depth measured by optical coherence tomography was also compared.

Results
We identified six RCTs involving 339 eyes that met the eligibility criteria for this meta-analysis. Conventional CXL resulted in significant better outcome in postoperative changes in best spectacle-corrected visual acuity (WMD=0.02; 95% CI: 0.01 to 0.03; p<0.001), however the small differences may not be clinically significant. There was no significant difference between the two groups for changes in maximum keratometry, thinnest corneal thickness, uncorrected visual acuity, spherical equivalent refraction, and corneal endothelial cell density (p=0.15, p=0.32, p=0.88, p=0.99, and p=0.88, respectively).

Demarcation line depth at 12 months after conventional CXL was deeper than that after accelerated CXL (WMD=- 102.25; 95% CI: -157.16 to -47.35; p=0.0003).

Conclusion
An accelerated CXL shows a comparable outcome and safety profile at 1 year follow-up, but it has less impact on improving best spectacle-corrected visual acuity, when compared to Dresden protocol. Overall, both methods similarly stop the disease progression.
Assessment of the association between in vivo corneal biomechanical changes after corneal cross-linking and depth of demarcation line in patients with progressive keratoconus.

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¹. Department of Corneal and External Eye Diseases, St. Paul’s Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom

Purpose
To evaluate the correlation between the stiffening effect measured with the Corvis ST (OCULUS Optikgeräte GmbH; Wetzlar, Germany) Dynamic Corneal Response Parameters (DCRs) and the depth of the demarcation line (DL) evaluated with anterior segment OCT.

Materials and Methods
Sixty-six eyes of 66 patients treated with CXL for progressive KC were included. DCRs obtained with the Corvis ST were assessed the day of CXL and after one month. DL was assessed 4 weeks post-CXL and it was defined as the posterior edge of the white-looking line present in the midstroma. A general linear model was employed to investigate the association between the change of Integrated Radius (1/R) after CXL, age and sex. Curve estimation analysis was done between Delta 1/R and the ratio between DL depth and the postoperative pachymetry (DLratio) to assess possible correlation.

Results
Curve estimation regression analysis showed no significant correlation between the Delta 1/R and the ratio between DLratio (R²=0.002, p=0.752). The absence of correlation between the stiffening effect and DLratio was confirmed by Mann-Whitney test that showed no significant difference in the stiffening effect in the patients with DL depth lower than 100 µm and all the rest of the patients (p=0.420 for 1/R and p=0.570 for Stiffness Parameter).

Conclusion
This study confirms that the DCRs of the Corvis ST are able to detect early changes in corneal biomechanics following CXL but proves that is no significant correlation between the stiffening effect and the depth of the demarcation line.
Automated detection and classification of corneal haze using optical coherence tomography in keratoconus eyes after cross-linking

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1. American University of Beirut Medical Center, 2. American University of Beirut

Purpose
To evaluate a proposed technology for offering objective grading and mapping of corneal haze as detected by corneal spectral domain optical coherence tomography after corneal cross-linking.

Materials and Methods
This was a retrospective study to evaluate corneal optical coherence tomography images performed on 44 eyes of 44 patients who underwent conventional corneal cross-linking at the American University of Beirut Medical Center.

Results
Overall average brightness of the cornea was markedly increased from 43.4%(±6.00) at baseline to 50.2%(±4.48) at 1-month, 47.9%(±4.45) at 3-months and 46.4%(±5.77) at 6-months with p values of <0.001, <0.001 and 0.005 respectively. In anterior stroma the average brightness significantly increased at 1, 3 and 6-months with p values of 54.8%(±3.98), 52.5%(±36.5.26) and 49.7%(±6.97) with p of <0.001, <0.001 and 0.003 respectively. In mid-stroma change was clinically significant at 1 and 3-months, while in posterior stroma it was only significant at 1-month compared to baseline (p = 0.003). Haze area was the largest at 1-month post-surgery in all regions; especially in the anterior 32.1%(±19.24) and mid-stromal regions 9.2%(±18.89); p of <0.001 and 0.001 respectively. In contrast, haze area in the posterior stromal region peaked at 3 and 6-months post-surgery. Similar comparison.

Conclusion
Anterior stromal haze was the greatest in intensity and area and it was present for a longer time span than mid and posterior stromal haze. At 12 months, the anterior stroma had still more haze intensity than preoperatively. This image-based software can provide objective and valuable quantitative measurements of corneal haze, which may impact clinical decision-making after different corneal surgeries.
Brillouin microscopy of human corneas before and after epi-on cross-linking

Dr. Doyle Stulting¹, Dr. Peng Shao², Dr. Amira Eltony², Dr. Jonathan Woolfson¹, Dr. Dimitri Chernyak³, Dr. Seok-Hyun (Andy) Yun⁴

¹. Woolfson Eye Institute, ². Harvard Medical School and Wellman Center for Photomedicine, Massachusetts General Hospital, ³. Intelon Optics, Inc., ⁴. Harvard Medical School and Wellman Center for Photomedicine, Massachusetts General Hospital and Harvard-MIT Health Sciences and Technology

Purpose
To study the stiffness of corneas with keratoconus before and after epi-on corneal cross-linking.

Materials and Methods
Regional corneal stiffness measurements of the cornea in 30 eyes of 30 patients with keratoconus were obtained with a Brillouin microscope before and 3 months after epi-on corneal cross-linking with riboflavin and UVA light.

Results
Brillouin measurements increased from 5.72 GHz preoperatively in the region of the cone to 5.75 GHz postoperatively (paired t-test, p<0.005). Median corneal stiffness increased from 5.73 GHz to 5.76 GHz (paired t-test, p<0.05), and spatial variation in corneal stiffness measurements decreased following CXL.

Conclusion
Brillouin microscopy is capable of detecting the corneal stiffening effect soon after a corneal cross-linking procedure that has been shown to increase vision and reduce the corneal curvature of corneas with keratoconus. It has the potential for early diagnosis of keratoconus and rapid evaluation of treatments that aim to stiffen the cornea.
Contact lens assisted cross-linking for progressive keratoconus with thin corneas about 47 cases

Dr. Yasser Rifay¹

¹ Dr. Rifay Ophthalmology Center

Purpose
The goal is to study the efficiency of contact lens assisted cross-linking in progressive keratoconus with thin corneas.

Materials and Methods
Prospective study including 47 eyes with progressive keratoconus with thin corneas (less than 400 microns), they all receive the same protocol of cross-linking (10 minutes) using VibeX Rapid, Avedro machine and Softlens contact lens.

We evaluate visual acuity, K max, thinnest location and demarcation line in 3, 6 months and one year.

Results
This study showed that contact lens assisted cross-linking in thin corneas is effective and safe with stabilisation of keratoconus in all case with very low rate of complications (one case of haze).

Conclusion
Contact lens assisted cross-linking is safe and effective procedure in thin corneas with progressive keratoconus.
Corneal cross-linking (CXL) with two different riboflavin solutions. A randomized, controlled trial.

Prof. Gerald Schmidinger¹, Dr. Niklas Pircher¹, Dr. Jan Lammer¹, Dr. Stephan Holzer¹

¹Medical University of Vienna

Purpose
Riboflavin solutions with HPMC instead of dextran have been shown to have less effect on corneal thickness during treatment. However, worse clinical outcomes have been postulated using this solution. This study was initiated to evaluate the clinical outcome of corneal cross-linking using riboflavin with 20% dextran or riboflavin with HPMC for the treatment of progressive keratoconus.

Materials and Methods
Eyes with progressive keratoconus were randomized to receive corneal cross-linking using riboflavin/20% dextran (Peschke D) or riboflavin/HPMC (VibeX Rapid). All irradiations were performed using 9mW/cm² (UVX-2000, Innocross). Pre-operative and postoperative visual acuity, topography, tomography and pachymetry were recorded. Main outcome measure was change in the maximum K-reading on the corneal surface [(K-max (D)]. Differences of the mean keratometric values in a zone of 2.5 mm (K2.5) around the K-max were evaluated as well. Additional outcome parameters were change in corrected distance visual acuity (LogMAR), pachymetry and higher order aberrations (HOA) given as RMStotal. The failure rate of each group was defined as the percentage of eyes with an increase in the maximum K-values and the K2.5-values of more than one diopter.

Results
Until today thirteen eyes treated with riboflavin 20% dextran and 12 eyes with riboflavin/HPMC have finished the 12 months follow up. Changes of all parameters after one year are given for Dextran group (mean ± standard deviation)/HPMC group (mean ± standard deviation). Kmax: -1.24 D ± 1.90 D/-0.56 D ± 1.90 D (p=0.50). K2.5: -0.71 D ± 0.96 D/-0.35 D ± 0.89 D (p=0.64). LogMAR: -0.05 ± 0.18/-0.12 ±0.17 (p=0.05). Pachymetry: -10 ± 21/+0.6 ±11 (p=0.24) and HOA: -2.11 ± 4.7/-1.21 ± 1.9 (p=0.72). The failure rate for Kmax was 0% in the Dextran group and 25% in the HPMC group. For K2.5 no failures were observed.

Conclusion
Eyes treated with riboflavin 20% dextran showed a more pronounced reduction of the K-readings than eyes treated with riboflavin/HPMC. These preliminary results support retrospective data that showed a weaker effect when eyes were treated with riboflavin/HPMC. Evaluating the maximum K-values as single parameter for success or failure of the treatment, the HPMC group showed a higher failure rate.
Corneal thinning and refractive index change monitored by optical coherence tomography and optical path length measurement during UVA-riboflavin corneal cross-linking

Dr. Xin Tan¹, Dr. Anant Agrawal², Dr. Daniel Hammer³, Dr. Ilko Ilev⁴

¹. US Food and Drug Administration/CDRH/OSEL

Purpose

Corneal Cross-Linking (CXL) using UVA irradiation with riboflavin photosensitizer has emerged as a new treatment paradigm for corneal ectatic disorders. Though standard protocol establishes the thickness threshold for protection of intraocular structures, the safety boundary has often been pushed with ongoing developments. Corneal thinning is an important safety concern especially for patients with thin corneas. In addition, the common clinical practice of assuming a constant refractive index in corneal thickness measurements has not been examined methodically for the CXL procedure, and actual increase in refractive index may exacerbate the corneal thinning problem.

Materials and Methods

In this study with an ex vivo bovine eye model, we monitored corneal thinning and corneal refractive index change using optical coherence tomography (OCT) and an adaptation of the optical path length method. CXL experiments were performed based on the standard protocol. A 1310-nm FD-OCT imaging system was used for ex vivo measurements of corneal thickness during the CXL procedure at three critical points – immediately after epithelial removal, after 30-minute riboflavin instillation, and after 30-minute subsequent UVA irradiation. We adapted the Sorin & Gray method (1992) for OCT measurement of the corneal refractive index by having a central corneal cut of 10-mm diameter extracted and placed on top of a reflective mirror as the reference plane.

Results

We found that the group refractive index of the bovine cornea changed significantly from epithelial removal to riboflavin instillation with value increasing from 1.377±0.005 after de-epithelization to 1.387±0.003 after instillation. Subsequent UVA irradiation did not bring further significant change to the refractive index with value of 1.388±0.008. The de-epithelized bovine corneas also underwent significant decrease in corneal stromal thickness (10-20%) with thinning of 95±29 µm after riboflavin instillation and further decrease (5%) with thinning of 42±19 µm after UVA irradiation. Corneal thickness changed from 829±56 µm after removal of epithelium to 726±52 µm after riboflavin instillation and further to 695±52 µm after subsequent UVA irradiation.

Conclusion

Our study highlights the importance of careful monitoring of corneal thickness especially after riboflavin instillation when the decrease is largest, and advocates corneal thickness measurements at critical points of CXL procedure as a safety precaution.
Customized CXL for keratoconus – 3-year results

Dr. Theo G. Seiler¹, Dr. Tobias Koller², Prof. Beatrice Frueh¹, Prof. Theo Seiler²
1. Inselspital, Universitätsspital Bern, 2. IROC

Purpose
To compare the efficacy of customized corneal cross-linking (CXL) with standard CXL with a follow-up of 3 years and to compare 1-year to 3-year results.

Materials and Methods
Forty eyes of 40 patients with documented progressive primary keratoconus were treated with customized CXL (n = 20) or standard CXL (n = 20) and followed for 3 years. Customized irradiation patterns had an irradiance of 9mW/cm² and radiant exposure levels ranging from 5.4J/cm² up to 10J/cm². The control group received homogenous irradiation with an irradiance of 9mW/cm² and a total energy of 5.4J/cm². Analyzed parameters were Scheimpflug tomographies, endothelial cell count, BSCVA and anterior segment OCT.

Results
Kmax showed significant changes within 3 years postoperatively for both groups with a significantly higher regression in the customized CXL subgroup (-1.9 ± 1.4D vs. -1.1 ± 1.4D). During the second and third postoperative year additional regularization occurred in the customized group but not in the standard group. Significant flattening (>1D) was observed in 12 out of 19 eyes (67%) in the customized CXL group and in 8 out of 19 (42%) in the standard group. A regression of >3D occurred in 7 eyes (39%) in the cCXL group and only in 2 eyes (11%) in the sCXL group.

Conclusion
Customized CXL appears to be as safe as standard CXL with stronger qualitative and quantitative flattening in Kmax and RI. Compared to the 1-year results there is a further improvement in corneal regularization in customized CXL after 3 years.
Early complications secondary to corneal cross-linking of keratoconus using two different riboflavin solutions

Dr. Stephan Holzer, Dr. Niklas Pircher, Dr. Jan Lammer, Prof. Gerald Schmidinger

1. Medical University of Vienna

Purpose
With limitations at late stages of the disease, corneal cross-linking (CXL) is the gold standard procedure for treating progressive keratoconus (KC). The purpose of this study was to assess early postoperative complications using two different commercially available riboflavin solutions for CXL in a prospective trial.

Materials and Methods
52 patients (m=41, f=11; OD=28, OS=24; mean age=26.4 years) with progressive KC were prospectively randomized at the Medical University of Vienna (Austria) for the use of two riboflavin solutions at CXL. Epithelium-off procedure and either 30 minutes (min) with Peschke D® (Peschke Trade GmbH, Switzerland) (PD, n=26) or 10 min incubation with VibeX Rapid™ (Avedro Inc., US) (VX, n=26) was conducted. A 10 min standardized UV-A radiation (UV-X™ 2000, IROC Innocross AG, Switzerland) (9mW/cm²) was performed. The early complication rate up to 3 months was assessed.

Results
14 (26.9%) cases of unwanted side effects were observed in total. Most of these cases were minor wound healing issues (13 patients / 25%), one case showed clinically significant scarring (1.9%; PD group) but no severe complication was seen in our study population. While the VX group presented with 3 delayed epithelial wound healings (11.5%) and 1 minor scar (3.8%), the PD group showed 6 delayed wound healings (23.1%), 1 sterile infiltrate (n=1), 1 case of subepithelial deposits, 1 early minor scar and 1 case with Salzmann degeneration. One patient (3.8%) suffered from halos and glare above the expected average. No case lost more than two lines in BCVA.

Conclusion
With only one case with clinically significant scarring and one case with photophobia (Peschke D® group) in our cohort, corneal Cross-linking, using either riboflavin solutions Peschke D® or VibeX Rapid™, seems to be a save method for the treatment of keratoconus. The preliminary data of this prospective trial suggest that VibeX Rapid™ results in lower early postoperative complications after CXL.
Effects of corneal cross-linking on tensile properties of posterior and anterior corneal flaps

Prof. Hamed Hatami-Marbini, Mr. Sandeep Jayaram
1. University of Illinois at Chicago

Purpose
Corneal cross-linking (CXL) is among commonly used treatments for stopping the progression of keratoconus. The primary objective of the present study was to characterize the stiffening effects of CXL on tensile properties of anterior and posterior corneal flaps at different hydration levels.

Materials and Methods
Anterior and posterior flaps were dissected from porcine corneas with a DSAEK system. The individual flaps were cross-linked at different hydration levels and their mechanical behavior was measured by conducting uniaxial tensile experiments. The average thickness of posterior groups was 845 µm, 650 µm, and 440 µm and average thickness of anterior groups was 670 µm, 540 µm, and 410 µm.

Results
It was found that anterior flaps were significantly stiffer than the posterior flaps. Furthermore, CXL procedure significantly improved biomechanical properties of anterior flaps (p < 0.05). Nevertheless, it did not have any significant effect on tensile properties of posterior flaps. Furthermore, except for the posterior flaps in 845 µm and 650 µm thickness groups, decreasing the hydration significantly increased the tensile modulus of all groups (p < 0.05).

Conclusion
The stiffening effect of CXL therapy significantly depends on the composition and microstructure of collagen lamella and proteoglycans throughout the corneal thickness.
Effects of drug formulation, supplemental oxygen, and UV delivery on epi-on CXL

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Purpose
Effective CXL requires sufficient levels of photosensitizer, oxygen, and UV in the stroma to induce therapeutic amounts of free radical formation. Simultaneous delivery of all three constituents is challenging with an intact epithelium. This study provides ex vivo measurements comparing stromal riboflavin loading, biomechanics, and topographic impact of two epi-on protocols using different paradigms for drug formulation, supplemental oxygen, and UV delivery.

Materials and Methods
This study was conducted in a laboratory setting using fresh, ex vivo porcine eyes. Eyes were partially de-epithelialized to 50 µm by gently wiping the cornea. A custom chamber allowed control of temperature, humidity, and delivery of oxygen. The first protocol used 0.25% riboflavin with BAC followed by 0.22% riboflavin without BAC. Supplemental oxygen at >90% purity was delivered to the anterior surface of the eyes. UV delivery was 30 mW/cm², 1 sec : 1 sec pulsing, and 10 J/cm². The second protocol used 0.50% riboflavin with 0.015% sodium iodide, room air, and UV delivery at 4 mW/cm², 15 sec : 15 sec pulsing, and 4.1 J/cm².

Stromal riboflavin loading was measured quantitatively with a custom confocal fluorescence microscope. Stiffness was measured using a biaxial extensiometer. Anterior curvature changes were measured using a Pentacam HR tomography system.

Results
Stromal riboflavin loading was higher with the first protocol, where BAC was included in the formulation. The second protocol where sodium iodide was included in the formulation showed lower levels of stromal riboflavin. Stiffening and flattening were also larger in the first protocol. This is likely due to a combination of increased riboflavin availability, increased stromal oxygen, and more effective UV delivery.

Conclusion
In ex vivo porcine eyes, a combination of BAC additive, increased anterior oxygen concentration, and 30 mW/cm², 10 J/cm² UV delivery with 1 sec : 1 sec pulsing gave improved stromal riboflavin levels, increased stiffening, and more pronounced flattening compared to an alternate epi-on approach.
Enhanced-fluence pulsed-light iontophoresis corneal cross-linking: 1-year morphological and clinical results

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Purpose

Materials and Methods
Prospective interventional pilot study including 24 eyes of 20 patients, 80% male, mean age 24.8 years (range 15-36 y). Iontophoresis with the Ricrolin+® solution was used for stromal imbibition. The treatment Energy Dose (Fluence) was optimized at 30% (from 5.4J to 7J/cm²) and UV-A power set at 18mW/cm² x 6.28 min of exposure time, pulsing the light 1 sec on/1 sec off with a total irradiation time of 12.56 min. Uncorrected distance visual acuity (UDVA), Corrected Distance Visual Acuity (CDVA), Scheimpflug Corneal Tomography data and Corneal OCT at baseline, 1, 3, 6, 12-months were evaluated.

Results
Statistically significant 12-months average data (p <0.05) showed UDVA decrease from 0.50 ± 0.10 to 0.36 ± 0.08 LogMAR, K max reduction from 52.86 ± 1.5 D to 51.49 ± 0.9 D, SAI decrease from 2.34±0.36 to 2.13±1.12 D, SI diminution from 4.22±1.01 to 3.56±0.90 D, Coma reduction from 0.25±0.05 to 0.14±0.06 µm. Corneal OCT showed an over 90% demarcation line detection at 295.8±20.2 µm depth on average in the 1st postop month.

Conclusion
The over 1-year results of EF I-CXL protocol demonstrate its capability to rise conventional I-CXL protocol efficacy by enhancing the UV-A Fluence and pulsing the UV-light thus compensating epithelium UV-A absorbance and partially oxygen consumption. Enhancing intraoperative oxygen delivery could another step forward increasing the iontophoresis-assisted epi-on CXL efficacy.
How do we calculate the exact pre-operative pachymetry POP during cross-linking epi-OFF?

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Purpose
If the interest of corneal topography is unquestionable on the diagnostic and therapeutically levels as well as the surveillance one, the input of epithelial mapping is gaining more and more importance thanks to the OCT input of the last generations in the analysis of epithelial pachymetry.

Materials and Methods
For two years all the patients suffering from paediatric or evolutive keratoconus are therefore candidates to CXL and have benefited from epithelial mapping.

Results
Over 100 patients suffering from known keratoconus have benefited from both a corneal topography by Pentacam and an epithelial mapping by OCT OPTOVUE.

The analysis looked at the central pachymetry analysis, thinnest pachymetry, the thickness of the corneal epithelium in front of the thinnest pachymetry.

The difference between thinnest pachymetry - Epithelial pachymetry: $TP - EP = POP$, on the facing page should be superior to $400 \, \mu m$. It is the per operative pachymetry “PPO” and if it is inferior to $400 \, \mu m$ the cross-linking epi-off must be assisted by a lens to reach the $400 \, \mu m$ safety microns required during the cross-linking epi-off procedures order to avoid endothelial toxicity.

In about 30% of cases and despite a central pachymetry superior to $400 \, \mu m$, the PPO calculated thanks to this method has helped to avoid post-CXL complications as the 400 safety microns has not been respected.

Conclusion
The analysis combined topography and epithelial mapping has allowed an accurate analysis both global and segmental variations of different corneal layers like corneal epithelium and the stroma in the keratoconus Our tale home message is the POP is very useful in CXL procedure.
Impact of stromal oxygen dynamics on high-irradiance epi-on cross-linking

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Purpose
Stromal oxygen affects the balance between Type I and Type II reactions during CXL. As oxygen is depleted, anaerobic reactions begin to dominate and cross-linking efficiency decreases. This effect is more pronounced with high irradiances (high oxygen consumption) and in epi-on procedures (low oxygen diffusion). This study provides ex vivo measurements comparing stromal oxygen dynamics, biomechanics, and topographic impact of high-irradiance CXL under normoxic, hyperoxic, and hypoxic conditions.

Materials and Methods
This study was conducted in a laboratory using fresh, ex vivo porcine eyes. Porcine eyes were first partially de-epithelialized by 50 µm to replicate the epithelial thickness of human corneas. A custom chamber was used to allowed control of temperature, humidity, intraocular pressure, and oxygen concentration. For hyperoxic experiments, the chamber was filled with >90% supplemental oxygen. For hypoxic experiments, the chamber was reduced to <5% oxygen.

Stromal oxygen was measured with a fiberoptic probe inserted into a laser-cut channel at a depth of 250 µm. Oxygen was continuously monitored before, during, and after UV illumination. A UV irradiance of 30 mW/cm², dose of 10 J/cm², and 1 sec : 1 sec pulsing were used, with and without application of supplemental oxygen.

For CXL experiments, eyes were dosed with a two-part trans-epi riboflavin formulation (ParaCel Part One/Two) and crosslinked with the same protocols described above. Stiffness was measured on 250 µm thick corneal segments using a biaxial extensometer. Anterior curvature changes were measured using a Pentacam HR tomography system.

Results
Stromal oxygen levels increase significantly when supplemental oxygen is provided at the anterior surface. This translates into increased CXL efficiency, greater corneal biomechanical strength, and more pronounced flattening hyperoxic environments compared to normoxic and hypoxic environments.

Conclusion
Delivery of supplemental anterior oxygen increases stromal oxygen availability, despite increased consumption and decreased diffusion in high-irradiance epi-on CXL protocol. Supplemental oxygen results in improved corneal stiffening and flattening in ex vivo porcine eyes.
Influencing factors on topographic outcome of corneal cross-linking for keratoconus

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**Purpose**
To identify factors that influence the topographic maximum keratometry (Kmax) after corneal cross-linking (CXL) for keratoconus (KC).

**Materials and Methods**
Retrospective review of all the files of patients (>18-yrs-old) who had CXL for KC (August 2007 to August 2017) with 1-year follow-up or more. We analyzed the influence of type of CXL (epi-on or -off and accelerated or non-accelerated procedures) and pre-operative age, gender, Kmax, central corneal thickness (CCT) and follow-up (FU) time on the final Kmax outcome (Kmax_{last} – Kmax_{pre}). A multivariate analysis and a stepwise linear regression after univariate analysis were performed using IBM SPSS version 24.

**Results**
Five hundred seventeen eyes were included with FU ranging from 12 to 120 months. Mean Kmax decreased from 54.07D±5.99 to 52.85±5.66D (p<0.01) in the last follow-up. CXL type (epi-on or -off), FU time, Kmax\_pre, and CCT had a statistically significant (p<0.05) influence on Kmax outcome. Age, gender and CXL time did not affect the outcome of Kmax (p=NS). Kmax\_pre was inversely correlated and CCT was directly correlated with final Kmax outcome (Kmax_{last} – Kmax_{pre}). A prediction model of Kmax_{last} was established based on the type of CXL procedure (epi-on/off), Kmax_{pre}, and FU time with coefficient of determination of 76.1%. Validation done with some other studies was within 1D margin.

**Conclusion**
CXL type (epi-on/off), pre-operative Kmax, CCT and FU time can affect the final outcome of Kmax.
Is corneal cross-linking treatment effective in stabilizing the corneal curvature during pregnancy in keratoconus patients?

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Purpose
To evaluate the effects of pregnancy on refractive and topographic parameters of keratoconus patients who were previously treated with corneal cross-linking (CXL).

Materials and Methods
24 eyes of 14 consecutive keratoconus patients who became pregnant at least 6 months after their CXL treatment with a minimum of 6 months post-partum follow-up period were included. The uncorrected and best corrected visual acuity, spherical equivalent, manifest astigmatism, corneal topographic parameters including keratometry (K) values, central and thinnest corneal thickness, topographic cylinder, anterior and posterior elevation were assessed before CXL, at last visit before pregnancy, at 3rd trimester of the pregnancy and at post-partum last visit.

Results
The mean age was 25.83 ±4.8 years at pregnancy. The mean time between CXL and conception was 12.41±5.1 months. The mean post-partum follow-up period was 27.6±13.3 months. There were no significant changes in the visual and refractive parameters, and corneal thickness with the pregnancy (p>0.05, for all). The mean Kmax significantly increased during pregnancy when compared to the one obtained at pre-pregnancy last visit (p=0.037). It decreased during the post-partum study period and became lower than the pre-CXL value at last visit (p=0.004). Similar with the Kmax, posterior elevation increased during pregnancy and decreased during the post-partum follow-up period, however the differences were statistically insignificant (p>0.05, for all).

Conclusion
The results of the present study revealed a reversible increase in the corneal curvature during pregnancy in keratoconus patients previously treated with CXL. Therefore, clinicians should be cautious to repeat the CXL in these patients and should wait during the post-partum period until the corneal curvature has been stabilized.
Is Pellucid Marginal Degeneration a variant of keratoconus or a different entity – structural, molecular and biomechanical changes and its impact on cross-linking

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Purpose
To elucidate the structural, biomechanical and molecular properties of Pellucid Marginal Degeneration (PMD) versus keratoconus (KC) and to see if PMD is a variant of KC.

Materials and Methods
PMD and KC are both corneal ectasias causing visual compromise, but with inherent differences. We studied 20 eyes of 10 PMD patients and 50 eyes of 25 KC patients by imaging, air-puff applanation, tear cytokines, confocal analysis and gene expression analysis. Differential CorvisST measurements were taken superiorly, centrally and inferiorly. The epithelium was collected separately from the ectatic area and the surrounding non-ectatic area and was analyzed later for gene expression analysis. The tears were collected on Schirmer’s strips, put in Eppendorf tubes and stored in our biorepository at -80°C. For analysis, the tears underwent flow cytometry and cytometric bead array.

Results
Confocal microscopy revealed a fibrotic component in the inferior ectatic area in PMD which was distinct from KC. Gene expression from the ectatic tissue and matched periphery showed LOX and collagen levels significantly higher in the ectatic area in PMD compared to the cone in KC. This was supported by the differences in biomechanics measured on Corvis ST.

Conclusion
This study shows that PMD and KC are probably different entities and not variants of the same disease as sometimes believed. These results may have huge impact on treatment planning and surgical outcomes of these diseases.
Long term results of CXL for corneal ectasia: Egyptian experience over 12 years

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Purpose
Long term results of CXL for keratoconus and post refractive surgery ectasia performed since 2006. Topographic, Tomographic and Refractive results demonstrated. Various techniques compared to determine efficacy, safety and stability of CXL. Analysis of factors like etiology, age, pre-operative Kmax and corneal thickness will be discussed in response to their effect on CXL.

Materials and Methods
Over 10 thousand eyes, different age groups and indications had CXL since 2006. Pre-operative evaluation: detailed history, refraction, topography and Tomography for inclusion and exclusion criteria. Standard epi-off CXL of 3 mW for 30 minutes was done. Along the years, variations in the technique were tried including: epi-on, accelerated and pulsed CXL using different systems. Postoperative evaluation and follow up was documented in most cases using the same pre-operative parameters for evaluation of CXL effect along follow up period cases with 10 years of follow up will be highlighted.

Results
98% of cases performed using our standard protocol showed stabilization of their ectasia along the follow up proved by serial topography, pachymetry, refraction and both uncorrected and corrected VA. 20–30% of cases showed continued effect of CXL manifested by progressive flattening and corresponding hyperopic shift over a period up to 5 years. Only 2% of cases showed No effect or recurrence of ectasia along the follow up. Repeated CXL was done in only 32 eyes that showed progression of ectasia after CXL. Analysis of the results based on etiology, age of patients, Kmax, corneal thickness and technique of CXL and patient behavior including eye rubbing will be discussed.

Conclusion
CXL is an effective technique to prevent the progression of corneal ectasia in both primary keratoconus and post refractive surgery ectasia. Pre-operative, operative and postoperative protocol should be followed to achieve and maintain effectiveness. Effect of CXL is progressive in many cases up to 5 years of follow up. Effect of age, Kmax, corneal thickness and eye rubbing should be considered to predict and maintain the efficacy and safety of CXL.
Management of post-LASIK ectasia

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Purpose
To report the clinical outcomes following treatment of post laser in situ keratomileusis (LASIK) induced ectasia.

Materials and Methods
This is retrospective case series of 7 patients (10 eyes), which developed post LASIK ectasia. In these cases of postoperative ectasia, the presented clinical signs were either, forme fruste keratoconus, thin cornea, posterior elevation map value >+15.0 µm or residual stromal bed <300 µm. In all cases, the flap was created using the Moria M2 mechanical microkeratome (average flap thickness 118.15±12.88 µm) and refractive error corrected using the Wavelight Allegretto excimer laser. All cases were treated with either corneal cross-linking (CXL) alone or CXL combined with PRK or CXL and phakic intraocular implant using the Dresden protocol and a slight modification thereof.

Results
Average pre-operative corrected visual acuity (CDVA) was 0.75 (±0.26) Snellen. Postoperative CDVA significantly increased to 0.86 (±0.13) Snellen (p=0.04, paired t-test). One eye lost three lines of its baseline CDVA (before ectasia) while all other eyes regained lines of CDVA. All cases remained stable during the follow up.

Conclusion
Several surgical procedures are used for the management of corneal ectasia. However, the best surgical approach should be determined based on the state of progression of the disease. Although ectasia remains a potentially devastating complication after refractive surgery, most patients can regain functional visual acuity with appropriate management and corneal transplantation is infrequently indicated.
Mega-dose dietary riboflavin and direct sunlight exposure in the treatment of keratoconus and post refractive surgery ectasia of the cornea – an update.

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Purpose
To determine whether high doses of dietary riboflavin and natural sunlight may induce therapeutic and topographic cross-linking in the cornea

Materials and Methods
Since our presentation at last year’s 2017 CXL conference, several new patients have been enrolled in our IRB study and additional investigators have added to the data set. The authors will update the data set with new findings, results and recommendations, including the effect of higher doses of dietary riboflavin, findings of higher amounts of astigmatism and ectasia treated successfully, and new treatment recommendations along with the introduction of a new IRB protocol inspired by last year’s CXL Experts’ Meeting for pediatric patients who show astigmatism with progressive myopia treated using high-dose dietary riboflavin and direct sunlight.

Following our original IRB protocol, and under the guidelines of the Declaration of Helsinki patient rights, patients were randomized to two groups. Group one taking 100 mg dietary riboflavin and Group two taking 400 mg or more dietary riboflavin. Both groups then went outside for 15 minutes daily walking vigorously facing the sun without sunglasses or contact lens wear. This was continued for 6 months, at which time patients were offered the option to continue or discontinue treatment. Visual acuity, refractive error, keratometry readings, topography based on refractive program of the Pentacam before and after treatment was recorded.

Results
14 patients completed 6 months or more of mega-dose dietary riboflavin therapy combined with 15 minutes of vigorous walking facing the sun. No adverse patient reactions to the dietary riboflavin was reported. The average cornea flattening measured on topography and keratometry readings was 1.2 Diopters, with a range from zero to 2.5 Diopters. The age of study patients ranged from 16 to 75 and included patients with a history of keratoconus, post LASIK and post PRK ectasia. One patient served as an unintended control as he neglected to remove his rigid gas permeable contact lenses prior to UV exposure and had no effect from therapy.

Conclusion
Our study suggests that ingestion of mega-doses of dietary riboflavin and ambient UV-light exposure may result in cross-linking and topographic and therapeutic flattening of the cornea in patients with keratoconus or ectasia.
Multiphoton tomography for accelerated-cross-linking follow-up

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Purpose
In this study, we propose to follow-up and assess the outcome of accelerated corneal cross-linking (A-CXL) based on corneal stroma autofluorescence (AF) using multiphoton tomography (MPT).

Materials and Methods
De-epithelialized human corneas were infused with 0.1% riboflavin solution for 20 min and irradiated with ultraviolet-A (\(\lambda = 365\) nm) for 10 min using an LED to perform A-CXL. The effect of the treatment on the tissue AF was evaluated using the multiphoton tomograph MPTflex (JenLab GmbH, Germany). Sample excitation was accomplished using an 80 MHz Ti:sapphire laser generating 100 fs pulses with a centre wavelength of 760 nm. AF images of the corneal stroma were acquired prior to A-CXL and after 2h, 24h, 72h, and 144h. Corneas without treatment and only infused with riboflavin were also monitored at these time points.

Results
The corneal stroma AF intensity and lifetime was significantly increased as soon as 2h after A-CXL and remained significantly higher after 24h, 72h, and 144h. The highest increase of both measurement parameters was observed for the anterior portion of the stroma, which correlates with the area where A-CXL was more effective and more crosslink bounds were formed. No significant alterations were observed after riboflavin application but without UV irradiation or for the control group.

Conclusion
MPT can be used to monitor A-CXL and the treatment's outcome may be determined sooner than with conventional clinical methods.
Novel chemical cross-linker for the cornea to treat keratoconus

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Purpose
To develop a chemical cross-linker to treat keratoconus that penetrates without removal of the epithelium, causes no toxicity to the cells while producing similar stiffening to the current riboflavin/UVA treatment

Materials and Methods
The cross-linker is composed of octanedioic acid (ODA), N-hydroxysuccinimide (NHS) and 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) which initiates the formation of amide bonds between carboxylic acid and amine groups. The solution was made up as a 1:1:1 molar ratio and applied to ex vivo pig, human normal and keratoconic corneal tissue for 15 minutes.

Post-treatment the mechanical properties were measured using a Linkam Stress Tester, histological analysis performed using H&E, TUNEL and Alizarin red staining, penetration measured using NHS-fluorescein and cell toxicity evaluated by harvesting and culture of the epithelial, stromal and endothelial cells from the tissue. Mass spectroscopy was used to analyze the proteins in the crosslinked cornea.

Results
The treated pig cornea increased in stiffness by approximately 70% and was similar to that of tissue treated with the standard riboflavin/UVA treatment. For healthy and keratoconic human tissue a 1.5-fold and a 3-fold increase in stiffness, respectively, was measured. Comparison of treated and control tissue stained with H&E and TUNEL showed no evidence of cell death or apoptosis, respectively, in the treated tissue. Alizarin red staining of the endothelium showed no evidence of toxicity. The NHS-fluorescein assay suggested the cross-linker had penetrated 500 µm into the pig cornea through an intact epithelium. Healthy cells were harvested and cultured from the epithelium, stroma and endothelium of treated pig and human tissue and stained for their appropriate phenotypic markers. Mass spectroscopy demonstrated cross-linked proteins including collagen α1, 2 and 6 as well as lumican, decorin and thrombospondin.

Conclusion
We have developed a chemical cross-linker that can stiffen ex vivo pig and human cornea to a similar extent to the current standard treatment, without removing the epithelium and without causing toxicity to the cells within the cornea.
The independent effect of various treatment modalities on cross-linking effectiveness studied in 670 eyes

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Purpose
To investigate the independent influence of variations in corneal cross-linking (CXL) techniques on treatment effectiveness one-year post-treatment in keratoconus patients.

Materials and Methods
This prospective longitudinal cohort study was conducted in a tertiary academic treatment center. Eight combinations of treatment modalities were assessed: two different CXL techniques (transepithelial and epithelium-off), seven different riboflavin formulations, and two different ultraviolet-A protocols (3 mW/cm² and 9 mW/cm²). Treatment modalities were compared with the Dresden protocol as a reference group using a multivariable linear regression analysis. Primary outcomes were the increase of maximum keratometry (Kmax) and mean keratometry (Kmean) at one-year follow-up. Secondary outcomes were uncorrected and corrected distance visual acuity, manifest refractive spherical equivalent, corneal thickness at one-year follow-up, and the rate of adverse events.

Results
670 eyes from 461 patients were treated. Overall, Kmax and Kmean decreased slightly (-0.02 D and -0.73 D respectively) one year after treatment. Four treatment modalities differed significantly from the reference standard in terms of Kmax and Kmean: the transepithelial group (+0.1±1.7 D, β 1.422, \( P = 0.001 \)) and (+0.4±1.1 D, β 0.844, \( P = 0.007 \)), one riboflavin formulation (Meran (-0.4±2.4 D, β 1.210, \( P = 0.02 \)) and 0.3±0.7 D, β 0.964, \( P = 0.001 \)) and both 9 mW/cm² protocols (VibeX Rapid (+0.4±1.0 D, β 1.751, \( P < 0.001 \)) and +0.3±0.6 D, β 0.756, \( P = 0.007 \)) and Collagex group (+0.1±2.2 D, β 1.170, \( P < 0.001 \)) and +0.2±0.9 D, β 0.610, \( P < 0.001 \)).

Overall, visual outcomes, spherical equivalent, and corneal thickness were similar in all treatment modalities. Infections were rare (1.6%), but a retreatment was necessary in 33.3% of transepithelial treatments.

Conclusion
Transepithelial cross-linking, the Meran riboflavin, and accelerated irradiation protocols appeared to be less effective in controlling keratoconus progression. Re-treatments were particularly eventful in the transepithelial treatment group. Therefore, we consider conventional 3mW epithelium-off CXL the gold standard for halting progressive keratoconus.
The results of the accelerated corneal cross-linking in initial stages of progressive keratoconus

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Purpose
For the treatment of initial stages of progressive keratoconus (CC) used UV cross-linking of corneal collagen (UltraViolet - Cross-linking - UV-X), which is officially approved by the “gold standard” treatment of this pathology since 2011. With the latest generation device (UV-X™ 2000 Avedro company) is possible to performed accelerated CXL, which allows in three times reduce the procedure time to 10 minutes.

Setting/Venue
A phase IV, open label, single arm, monocentric study conducted in Ukraine.

Materials and Methods
75 patients, 110 eyes (45 men and 30 women; age range 12 to 57 years, median 25 years) with KC II (46%) and III (54%) were treated by accelerate CXL procedure.

At inclusion, all patients underwent standard ophthalmologic examination for KC assessment including biomicroscopy, refractometry, keratogram, pachymetry, uncorrected (UVA) and best corrected visual acuity (BCVA). The UV-X procedure was performed using a UV-X™ 2000 device with a radiation power of 9mW/cm².

Data were collected preoperatively and postoperatively at the 3-month, 6-month and 1-year after CXL procedure. De-epithelization of the cornea was carried out with diameters of 7.0; 7.5; 8.0 mm in accordance with the keratogram data.

Results
Epithelialization of the cornea surface was from 3 to 5 days (4.0 ± 0.7 SD days). The degree of astigmatism after 12 months decreased by 1.4D (2.9 ± 1.5 SD) (p=0.000). The refractive power of the cornea (Kmax test) after 12 months it decreased by 3.2D (55.4 ± 6.7 SD), p = 0.02. The thickness of the cornea (thinnest local) after 12 months increased in 8.8nm to 464.3 ± 31.2SDnm (p = 0.000).

After 12 months UVA increased in 68 eyes (98.5%) from 69, BCVA increased in 62 (89.8%) from 69 eyes (p=0.001). No intraoperative complications occurred.

Conclusion
The procedure of accelerated CXL of the cornea on the UV-X™ 2000 Avedro device is comfortable and safe for patients and allows stabilizing the keratoconus, achieving an increase visual acuity and reducing the degree of astigmatism in the period up to 12 months postoperative follow-up.
Translational impact of lysyl oxidase (LOX) on cross-linking/refractive surgery and allied novel point-of-care diagnostic kit.

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Purpose
To investigate the role of lysyl oxidase (LOX), an endogenous cross-linker on refractive surgery/cross-linking outcomes and the relevance of point-of-care diagnostic kit to determine LOX status in clinical practice.

Materials and Methods
LOX expression was studied in 3 group of patients.

Group A: LOX and collagens (COLIA1 and COLIVA1) gene expressions in debrided corneal epithelia of KC patients (90 eyes) undergoing cross-linking (CXL) and control subjects (52 eyes) without KC but undergoing photorefractive keratectomy (PRK) were measured by qPCR. LOX activity was measured in the tears as well. Group B: LOX expression was measured in epithelium of KC patients (42 eyes) undergoing CXL. Postoperative outcomes were correlated to pre-op LOX status.

Group C: LOX expression was measured in preserved lenticules of a single patient with normal pre-op topography developing ectasia post-SMILE (PSE) and in controls (did not develop ectasia, n=25). Antibodies specific to LOX were raised and tested for their cognate affinities.

Results
Group A: Significant (P<0.05) reduction in LOX expression and activity was observed in corneal epithelium and tears of KC patients, which also correlated with disease severity.

Group B: Pre-operative expression of cone specific LOX and COLIVA1 were significantly (P<0.05) higher in cases with positive cross-linking outcomes.

Group C: Reduced expression of LOX (0.57) and COLIVA1 (0.5) was observed in PSE eyes compared to controls. LOX specific antibodies were raised that are being adapted to a multiplex detection platform.

Conclusion
Reduced pre-existing LOX and collagen expression levels may predispose clinically healthy eyes undergoing refractive surgery to ectasia, due to deficient endogenous cross-linking activity. Similarly, in keratoconic eyes, it may lead to suboptimal cross-linking outcomes. Hence, developing a point-of-care kit to measure these biomarkers in pre-operative tears will improve patient selection, risk evaluation and evidence-based prediction of surgical outcomes.
When corneal cross-linking additionally and dramatically improves the visual acuity, a pleasant surprise!

Ms. Rawya Diab, Ms. Honaida Elsheikh
1. Sudan Eye Center

Purpose
This case report aims at describing one of the additional benefits of corneal cross-linking "CXL", using riboflavin and UV-A; which is considered as the gold standard management of keratoconus. It works by increasing the stromal biochemical stability, halting disease progression. Many studies have assessed the efficacy and safety of CXL, yet until now, the exact mechanism hasn't been well understood. The corneal responses were found to vary considerably; improvements in topographic parameters and vision were reported.

Materials and Methods
The first case is a 27 years old male; VA: counting finger OU; best VA 6/36 OD, 6/24 OS, refraction: -16.00 D sph/-10.50 D cyl OD, -14.50 D sph/-7.5 D cyl OS.

The second case; a single eyed 25 years male; VA: 1/60, no reflex and no improvement with spectacles. Both were diagnosed as keratoconus, underwent conventional epi-off CXL and followed up.

Results
1st patient best VA: 6/12 OD, 6/6 OS; spectacles: -5.00 D sph/-4.50 D cyl OD; -1.00 D Sph/-1.5 D cyl OS, 2nd patient; best VA: 6/6, spectacles: -5.50 D cyl.

Conclusion
This 3 to 7 Snellen lines improvement in vision is remarkable. The exact mechanism remains to be elucidated; could it be related to the patient’s corneal characteristics; its thickness; contour or its healing properties; or it might be linked to the riboflavin and the UV-A; or some external factors. Future studies should be directed towards pointing out what factors lead to such an added advantage. And; indeed; for a better outcome those factors should be addressed and considered, particularly when doing combined procedures with CXL.
Accelerated corneal cross-linking: Faster, higher, but which protocol is biomechanically stronger?

Mr. Philip Jaycock
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Purpose
The aim of the present study was to compare the visual, refractive and topographic outcomes in patients with progressive keratoconus treated with different accelerated corneal cross-linking treatment protocols for patients from the South West of England at Bristol Eye Hospital, United Kingdom.

Materials and Methods
Baseline and postoperative visual acuity, manifest refraction, corneal topography and pachymetry were evaluated and compared.

In Group A: patients underwent 9 mW/cm² (10 minutes) continuous wave corneal cross-linking procedures.

In Group B: patients underwent 30 mW/cm² (8 minutes [1 second on and 1 second off]) pulsed wave corneal cross-linking procedures.

Results
380 eyes underwent corneal cross-linking procedures for progressive keratoconus between 2013 and 2017 inclusive.

In Group A: 96.7% of eyes showed stabilisation of keratoconus at 12 months postoperatively.

In Group B: 91.7% of eyes showed stabilisation of keratoconus at 12 months postoperatively.

The changes in uncorrected visual acuity, distance corrected visual acuity, astigmatism and corneal thickness were compared.

The National Institute for Health and Care Excellence (NICE) audit criteria for photochemical corneal cross-linkage using riboflavin and ultraviolet-A for keratoconus and keratectasia was used to compare and contrast outcome data for 9 mW/cm² (10 minutes) continuous wave and 30 mW/cm² pulsed wave corneal cross-linking protocols.

Conclusion
Accelerated 9 mW/cm² (10 minutes) continuous wave and 30 mW/cm² (8 minutes [1 second on/1 second off]) pulsed wave corneal cross-linking protocols are safe and effective in stabilising keratoconus.

These findings demonstrate biomechanical stability of accelerated corneal cross-linking protocols cross-linking at 1 year postoperatively.
CXL Plus
(Combination procedures)
A novel method to study Bowman's layer topography - A paradigm shift in understanding the corneal surface

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Purpose
To describe a novel method of computing topography and aberrations of the corneal surface and Epithelial-Bowman’s interface using AS-OCT and comparing this with Bowman's layer topography measured after epithelium removal.

Materials and Methods
25 normal and 30 KC eyes were analyzed using undistorted AS-OCT (12 scans) and Pentacam HR. Curvatures for OCT was calculated from the detected Anterior corneal surface (ACS) and Epithelium Bowman’s Interface (EBI) edges on the scans. Similarly, curvatures of the same ACS were obtained from Pentacam (OCULUS Optikgeräte GmbH, Germany). Wavefront aberration was also analyzed by ray tracing on OCT (ACS and EBI) and Pentacam data (ACS only). Manual epithelium removal of 30 KC eyes was done during cross-linking by a single surgeon and topography was repeated intraoperatively (intraop) to manually measure Bowman's topography. Paired t-test and ANOVA was used for statistical comparisons.

Results
Higher and lower order aberrations were greatest for the EBI followed by the anterior corneal surface in KC eyes (p<0.05). Kmax of the interface was steeper than the anterior corneal surface by 1D (p<0.05). The mean K1, K2 and Kmax (D) of Bowman’s topography measured intraop and derived from pre-op OCT images were similar (48.8±1.58, 48.1±1.59; 55.3±2.05, 54.7±2.27 and 56.4±2.04, 55.8±2.34 respectively).

Conclusion
This study presents a novel, non-invasive method for "virtual de-epithelization" using OCT, where no physical removal of epithelium is required. This method is accurate and comparable to manual de-epithelization method. This tool can be useful for pre-operative planning of transepithelial procedures and customized corneal cross-linking in keratoconus.
Athens protocol after femtosecond-assisted intracorneal ring implantation

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Purpose
To report safety and efficacy on visual outcomes and manifest refraction after Athens Protocol (same day surface ablation + corneal cross-linking) in patients with ectasia who previously underwent femtosecond-assisted intrastromal corneal ring implantation (fs-ICRS).

Materials and Methods
We retrospectively evaluate thirty-two eyes of 31 patients submitted to the Athens Protocol procedure 1 to 36 months after fs-ICRS with average follow-up of 21.4 ± 13.4 (6 to 52) months. All eyes had ICRS position evaluated by FD-OCT prior to the Athens Protocol procedure in order to assure at least 200μm of residual stroma over the ICRS after ablation. Epithelial healing was investigated. Pre- and post-operative uncorrected and corrected distance visual acuity (UDVA and CDVA, respectively), and manifest refraction were compared by non-parametric Friedman test.

Results
Complete epithelial healing was observed in all eyes within the first 7 days after Athens Protocol. No eye lost CDVA after Athens Protocol following fs-ICRS. All variables had a statistically significant improvement between the pre-operative and the last observation time-points (p<0.01). CDVA improved from logMAR 0.45 ± 0.20 (0 to 1) in the pre-op to logMAR 0.23 ± 0.21 (0 to 1) in the final postop (p<0.00001), manifest astigmatism improved from -4.96 ± 2.27 (-8.25 to -1) D to -2.66 ± 2.0 (-8 to 0) D (p<0.00001) and spherical equivalent improved from -5.89 ± 4.53 (-20 to -0.5) D to -3.55 ± 3.94 (-16.5 to 1.25) D (p=0.00053).

Conclusion
There is a synergistic additive effect of the Athens Protocol following fs-ICRS which was considered a safe and efficient procedure to improve visual acuity for patients with ectasia. Studies considering a longer follow-up are needed as guidelines for pre-operative planning and amount of stromal thickness over the ICRS estimation.
Case Report: Allograft lenticule onlay implantation with PTK after CXL in KC treatment

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Purpose
To report outcome of KC case after allograft lenticule onlay (Allotex) implantation with PTK immediately after CXL treatment for regularisation of corneal topography.

Materials and Methods
22 years old, male KC patient, uncorrected visual acuity (UCVA) was 0.3 and there was no increase with refractive correction. Mean K value was 48.4 D and thinnest pachymetry was 383 microns. Allograft lenticule (3 mm diameter, 20 µm) only with PTK ablation (5 µm – Visix S4, CustomVue S4IR, Abbott Medical Optics Inc., Santa Ana, CA, USA) was performed immediately after epi-on CXL with intrastromal riboflavin injection.

Results
There was increase in UCVA from 0.3 to 0.4 after 1-month follow-up. Mean K value was increased from 48.4 D to 50.0 D postoperative 1 month. Increase in mean K value was 1.6 D with more regular topography. There was no complication after treatment.

Conclusion
Allograft lenticule onlay implantation with PTK immediately after CXL treatment can be performed alternatively for regularisation of topographic surface in KC eyes. Long term follow-up and larger series are necessary to understand efficiency and safety of treatment.
Combined epithelium-off topography-guided photorefractive keratectomy and corneal cross-linking

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Purpose
To present the clinical outcomes of combined photorefractive keratectomy guided by epithelium-off corneal topography (epi-off-tPRK) and corneal cross-linking (CXL).

Materials and Methods
Retrospective case series analysis of 13 eyes, of 11 patients, with progressive keratoconus submitted to combined epi-off-tPRK and CXL, according to the Dresden protocol. All patients had the epithelium removed with an automated Amoils brush before corneal topography (WaveLight® Topolyzer™ Vario Diagnostic Device) was performed. The main outcome measures were: best uncorrected visual acuity (BUVA), best corrected visual acuity (BCVA), spherical equivalent, keratometry readings (K1, K2 and Kmax), central pachymetry (CP) and corneal tomography anterior curvature maps (CTACM) (Pentacam® - OCULUS, Wetzlar, Germany) – obtained preoperatively and at 1,3, 6 and 12 months postoperatively.

Results
Mean preoperatively BUVA increased from 0.28 ± 0.15 to 0.59 ± 0.27 at 12 months postoperatively (p<0.05). Mean preoperatively BCVA increased from 0.71 ± 0.11 to 0.78 ± 0.23 at 12 months postoperatively (p<0.05). Mean preoperatively Kmax decreased from 57.81 ± 5.90 to 52.61 ± 5.95 at 12 months postoperatively (p<0.05). There was no statistical significant difference between mean preoperatively K1 and K2 and at 12 months postoperatively. Mean CP preoperatively decreased from 469 ± 50.55 to 425 ± 46.79 at the 12-month follow-up. Postoperatively CTACM revealed significant regularization. All patients developed some degree of corneal haze postoperatively.

Conclusion
Combined epi-off-tPRK with CXL allows a precise regularization of the anterior corneal surface with visual acuity improvement, avoiding the masking effect of the corneal epithelium in keratoconus. This innovative approach seems to be safe and promising in the treatment of keratoconus.
Combined SMILE and CXL for moderate to high myopia in patients with thin or steep corneas

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Purpose
To evaluate efficacy, predictability, safety and stability of SMILE and CXL for moderate to high myopia in patients, with thin or steep corneas, not candidates for PRK, LASIK or phakic IOLs. SMILE and CXL combination augments remaining corneal tissues and provides added support thus minimizing risk of future ectasia in young patients

Materials and Methods
Prospective case series of 118 eyes of 66 patients. Inclusion criteria: Abnormal topography (very steep, skewed or asymmetric) and/or thin corneas < 500 µm. Stable refraction and topographic findings for 1 year. BCVA >0.7 and age >21 years. Refraction, topography, tomography, IOP and biomechanics of cornea. SMILE preformed with 100 µm cap and 270 µm residual bed thickness. Lenticule removal, followed by intra-pocket injection of isotonic riboflavin then 3 min 30 mw/cm² UV accelerated CXL. Postoperative refractive, VA (UCVA & BCVA) and tomography. Biomechanics using Corvis ST, correlating IOP and deformation amplitudes.

Results
Mean patient age was 29.4±5.63 (22-35 years). Mean pre-operative UCVA 0.13±0.08 and 0.82±0.13 postoperative. Mean pre-operative refraction was -3.97±1.87 D sphere (range -6.0 to - 1.25 D) and -2.85 D cylinder (range -0.75 to -4.25 D) Mean postoperative SER was -0.14±0.73 D (range -1.25 to +1.5). Mean astigmatism was -0.18 ± 0.45 D. 72% of eyes within ± 0.5 and 89% within ± 1.0 D. 1 eye lost 1 line of BCVA and 1 eye lost 2 lines due to haze. Some patients presented intrastromal haze that improved during the follow-up. Mean deformation amplitude was 1.38 mm ±0.29 pre-op. to 1.19 mm ±0.29 postop while pre and postoperative IOP showed no significance.

Conclusion
Combined SMILE and CXL is Safe, Effective, Predictable and Stable option for patients where LASIK or intraocular surgery cannot be performed. SMILE alone affects corneal biomechanics less but still carries risk of ectasia in young patients with thin corneas, abnormal topography (skewed or asymmetric astigmatism). When combined with CXL, remaining tissues are augmented reducing risks of future ectasia. Further follow-up and larger samples are needed to prove validity of such hypothesis.
Complications of combined CXL and PRK

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Purpose
To report complications following combined CXL and PRK [CXL/PRK] for keratoconus [KC] eyes.

Materials and Methods
We report 19 eyes of 13 KC patients with complications post-CXL/PRK. The group comprised 7 females and 6 males between the ages of 19 to 37 years. CXL/PRK was done between the years 2009-2017 in 5 locations worldwide.

Results
Pre-CXL/PRK the KC was stable in 7 patients, progressing in 2 patients and stability was not reported in 4 patients. Prior to treatment the BCVA was 0.8 or better in 8 eyes, 0.5 or better in 13 eyes and not documented in 6 eyes. Post-CXL/PRK severe infections occurred in 4 eyes of 2 patients. Remarkable scarring was observed in 16 eyes of 11 patients with wide range of corneal flattening. In 3 eyes of 2 patients significant corneal irregularities were observed without scarring. 17 eyes lost lines of BCVA. 4 eyes of 3 patients underwent penetrating keratoplasty. 2 eyes with corneal scars kept the pre-operative BCVA.

Conclusion
CXL/PRK is not recommended in KC patients with good and functional vision and in cases of stable KC.
Concurrent versus sequential treatment with corneal cross-linking and intracorneal ring segments (Intacs) for keratoconus

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**Purpose**
To assess outcomes, safety, and efficacy, of corneal cross-linking (CXL) and intracorneal ring segments (Intacs) used adjunctively, in concurrent and sequential surgery.

**Materials and Methods**
A prospective, randomized, clinical trial was performed in a cornea and refractive subspecialty practice. One-hundred ninety-eight eyes of 198 patients were randomized to one of two groups: Intacs first, immediately followed by CXL during the same session (n=104), or Intacs followed by cross-linking 3 months later (n=94). Outcomes included change in maximum keratometry (K_max) and topographic inferior-superior (I-S) difference, maximum flattening of topographic K, and changes in uncorrected (UDVA) and corrected distance visual acuity (CDVA) analyzed in the entire cohort, in the two randomized groups, and in subgroups stratified to Intacs size and placement. Patients were followed for 6 months.

**Results**
At 6 months, there was no significant difference between the sequential and concurrent groups in any of the outcomes analyzed. Overall K_max decreased by an average of 2.5 D, I-S difference improved by 3.9 D, and there was an average maximum flattening of 7.5 D. UCVA improved 2.0 logMAR lines, on average, and CDVA improved 1.1 lines. There were 6 clinically significant adverse events (2 concurrent, 4 sequential). These included 2 cases of infectious keratitis, 3 cases of inflammation around the Intacs segments, and 1 case of glare symptoms requiring explantation.

**Conclusion**
Corneal cross-linking and Intacs can be used adjunctively with substantial improvement in corneal topography, and with a similar safety profile to each procedure performed alone. Sequential vs. concurrent treatment with Intacs and CXL does not appear to impact clinical outcomes.
Corneal UV-light cross-linking promotes high-risk corneal graft survival by regressing mature corneal lymphatic and blood vessels

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1. University of Cologne, 2. Semmelweis University

Purpose
Pathological corneal vessels contribute prominently to the immune response and further cause graft failure. However, the indispensable need to regress pathological corneal vessels is still unmet in clinic. The purpose of this work is to assess whether corneal UV-light cross-linking (CXL) can succeed in regression of corneal pathological lymphatic and blood vessels, and thereafter promote graft survival in high-risk keratoplasty.

Materials and Methods
The effect of UV-light CXL using riboflavin and UVA on pre-existing mature corneal vessels was examined in mice. Corneas were isolated post-CXL, and double stained with CD31 and LYVE-1 to assess the effect of CXL on corneal blood and lymphatic vessels, respectively. In addition, CD45+ cells and macrophages were quantified post-CXL. After allogenic corneal transplantation, graft survival proportions were graded between high-risk recipients with and without prior CXL. Corneal histology was performed. Corneal epithelial regularity and defect size were also examined.

Results
UV-light CXL using UVA irradiation and riboflavin application regressed both pre-existing lymphatic and blood vessels significantly (n=5, p<0.05). Colocalization of TUNEL+ signal and CD-31 or LYVE-1 staining were detected in CXL treated inflamed corneas. Macrophages and CD45+ cells were significantly decreased in CXL treated corneas (n=5, p<0.05). Furthermore, long-term graft survival was significantly improved (n=12, p<0.05) in high-risk prevascularized recipients with preoperatively CXL treatment. Tregs in draining lymph nodes were upregulated (n=12, p<0.01) in CXL treated mice post keratoplasty. Additionally, no notable effect of CXL was observed on corneal re-epithelialization process and corneal regularity. CXL also reduced keratocyte density and corneal thickness without affecting corneal endothelial cells depending on the duration of CXL application.

Conclusion
UV-light CXL is demonstrated here as a novel method to regress both mature pathological lymphatic and blood vessels in corneas. Furthermore, the pre-operative CXL is shown for the first time to be prominently effective on promoting graft survival in subsequent high-risk corneal transplantation. This study should broaden the clinical use of CXL and may contribute to the development of new therapies in other immune diseases with pathological ingrowth of lymphatic and blood vessels.
Sectorial PTK+CXL for keratoconus treatment

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Purpose
To present a case of a keratoconic patient who underwent epithelial removal with transepithelial phototherapeutic keratectomy (t-PTK) sectorial type (covering the cone only) using high tech solution laser system followed by corneal cross-linking (CXL) 10J with riboflavin and ultraviolet-A (UVA) irradiation.

Materials and Methods
Clinical case audits series.

Results
9 of 9 patients’ eyes with keratoconus underwent CXL (18 mW for 10 minutes which equal to 10.8 J) treatment after sectorial epithelial removal with t-PTK (covering the cone only) using a high-tech solution system.

No intra or early postoperative complications were found. Patients were observed for one year postoperatively. Mean SIF (Symmetry Index Font), SIB (Symmetry Index Back), KVF (Keratoconus Vertex Front) Kmax, total HOA (High Order Aberration), coma, uncorrected visual acuity (UCDVA), Best spectacle - Corrected Visual Acuity (BSCV), and demarcation line observed in Optical Coherence Tomography (OCT) were compared preoperatively and at one year postoperatively.

Results
The mean SIF pre-operatively was $8.98 \pm 4.99$ D and one year postoperatively started to be $5.97 \pm 3.24$ D; mean of SIB improved from $2.56 \pm 1.29$ D to $1.99 \pm 1.35$ D after one year, meanwhile the mean of BCVF improved from $5.34 \pm 2.71$ D to $4.27 \pm 2.64$ D. Mean Total HOA pre-op was $3.59 \pm 1.64$ Eq.D and after one year post-op was $2.91 \pm 1.42$ Eq.D, mean Coma pre-op was $2.87 \pm 1.61$ Eq.D and after one year post-op is $1.83 \pm 1.57$ Eq.D, mean of UDVA pre-op improved from $0.29 \pm 0.28$ Decimal to $0.59 \pm 0.29$ Decimal, mean CDVA improved from $0.43 \pm 0.39$ Decimal to $0.69 \pm 0.31$ Decimal, mean KVF pre-op was $57.22 \pm 28.77$ µm and after one year post-op was $47.00 \pm 25.77$ µm, mean of Kmax pre-op was $66.00 \pm 13.17$ D and after one year post-op is $59.56 \pm 13.59$ D.

Conclusion
Sectorial epithelial removal with t-PTK before CXL could improve patient’s visual outcome by reducing post-op high order aberration, post-op K reading and reducing post-op pain, rehabilitation period.
PACK-CXL For Keratitis
In vivo and ex vivo assessment of corneal endothelium and limbal stem cell niche following Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT).

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1. Bascom Palmer Eye Institute

Purpose
Rose Bengal Photodynamic Antimicrobial Therapy (RB-PDAT) is a novel potential treatment for progressive infectious keratitis. The purpose of this study was to evaluate the effect of RB-PDAT on keratocytes, endothelium and limbal stem cell (LSC) niche, as well as long-term follow up with anterior segment OCT (AS-OCT) and confocal microscopy.

Materials and Methods
Rose Bengal solution (0.1% RB in BSS) was applied to the right cornea of rabbits for 30 minutes and then irradiated by a custom-made green LED light source (525nm, 6mW/cm²) for 15 minutes (5.4J/cm²). Three rabbits were sacrificed and enucleated after 24 hours. TUNEL assay and immunohistochemistry for endothelium and LSC viability were performed on whole mounts and frozen sections in treated and control eyes. LSC of both eyes were isolated and cultured to perform MTT viability and proliferation, as well as scratch wound healing assays under time-lapse microscopy. A second group (N=3) was followed for 36 days post-treatment with AS-OCT with fluorescence and TUNEL assay was performed on these corneal sections.

Results
TUNEL assay demonstrated superficial Rose Bengal penetration with associated cellular apoptosis in up to 1/3 of stromal thickness on frozen sections and showed no endothelial cell death following treatment on corneal whole mounts. Immunohistochemistry of LSC displayed no structural difference between both eyes. Cells isolated from control and treated eyes demonstrated no difference in LSC proliferation rates and cell migration after 24 hours. AS-OCT evidenced cross-linking demarcation line and Rose Bengal fluorescence in all treated eyes after 36 days of treatment. Rose Bengal fluorescence could still be observed in the corneal stroma yet there was no evidence of sustained cytotoxic effect with TUNEL at this time point.

Conclusion
Our data suggests that RB remains in the corneal stroma after treatment, and even though penetration of the Rose Bengal was said to be superficial, the oxidative stress produced by RB-PDAT seems to reach deeper into the corneal stroma. Nevertheless, our results indicate RB-PDAT is safe on the corneal endothelium and has no effect on limbal stem cell viability or function.
PACK-CXL as adjuvant treatment for acanthamoeba keratitis. A case study.

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Purpose
To describe the outcome of adjuvant photoactivated chromophore for infectious keratitis (PACK-CXL) used to treat an advanced form of Acanthamoeba keratitis (AK) diagnosed several months after initial presentation.

Materials and Methods
An otherwise healthy 24-year old female presented with a severe unilateral keratitis. The diagnosis eluded clinicians for several months and when finally confirmed as AK, anti-amoebic therapy was instated and only appeared to be effective after PACK-CXL.

Results
In this case of advanced AK, PACK-CXL treatment given adjuvant to medical anti-amebic therapy resulted in lasting pain relief and re-epithelization and eradication of the Acanthamoeba parasite.

Conclusion
Given adjuvant to anti-amoebic medical treatment PACK-CXL might be a useful alternative in treating typically refractory advanced AK. A thesis strongly supported by slit lamp and confocal microscopic examinations prior and post-CXL in this case.
Visual outcomes and graft survival rates of optical corneal transplants after Rose Bengal Photodynamic Antimicrobial Therapy as adjunctive treatment for infectious keratitis.

Dr. Jaime Martinez Martinez1, Dr. Andrea Naranjo1, Dr. Alejandro Arboleda1, Ms. Heather Durkee3, Ms. Mariela Aguilar1, Dr. Nidhi Relhan1, Dr. Neda Nickpoor1, Dr. Darlene Miller1, Dr. Guillermo Amescua1, Dr. Jean-Marie Parel1

1. Bascom Palmer Eye Institute

Purpose
To describe corneal graft survival and visual outcomes of patients that underwent optical corneal transplantation after the use of Rose Bengal Photodynamic Antimicrobial Therapy (PDAT) as treatment for infectious keratitis resistant to standard medical treatment.

Materials and Methods
Retrospective chart review of all patients who underwent optical corneal transplantation after treatment with Rose Bengal Photodynamic Antimicrobial Therapy (PDAT) for progressive infectious keratitis unresponsive to standard medical therapy at Bascom Palmer Eye Institute from January 2016 through March 2018. Rose Bengal PDAT was performed by applying a solution of Rose Bengal (0.1% or 0.2% RB in BSS) to the de-epithelized cornea for 30 minutes followed by irradiation with a 6mW/cm² custom-made green LED source (525nm) for 15 minutes (5.4J/cm²).

Results
A total of 9 eyes (70% female and 30% male) were treated. Mean age was 32 years (range 17–83 years). Sixty percent (5/9) of cases had confirmed Acanthamoeba keratitis, Fusarium was identified in 20% (2/9) and 10% (1/9) had Pseudomonas aeruginosa. One patient had no confirmed microbiologic diagnosis. Seven patients had optical penetrating keratoplasty (OPK) and two patients had Deep anterior lamellar keratoplasty (DALK). Concomitant cataract extraction with intraocular lens implantation along with the OPK was performed in 2/9 cases. One patient developed glaucoma after surgery and was treated successfully with a glaucoma drainage device. Postoperative procedures after corneal transplantation was performed in 4/9 cases (3 cases had cataract extraction with intraocular lens implantation and one case had tarsorrhaphy due to exposure keratopathy) without any complications. Mean time of follow-up was 6 months (range: 0.25 to 11) after corneal transplant. No graft failure or rejection was seen on follow up and all corneal grafts were clear at last follow up. Six eyes (70%) achieved a BSCVA of 20/40 or better.

Conclusion
Our experience suggests good visual outcomes and graft survival following corneal transplantation in eyes that have undergone Rose Bengal PDAT as an adjunct therapy for infectious keratitis.
Refractive CXL
An *in situ* UV polymerised artificial cornea for “custom smile” surgery

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¹ University of Crete

**Purpose**
To study the optical and mechanical properties for an *in situ* formed new cornea surface as a referral plane for the intrastromal cut by a femtosecond laser. The aim is to generate a custom interface cut with identical shape with the surface of the cornea.

**Materials and Methods**
We use a special biocompatible gel with the same optical properties with the cornea, in a liquid form and apply on the cornea surface. We apply on the gel, a cone used for the femto laser intrastromal cut, with a given curvature in order the interface space between cornea and cone to be filled with the gel. The time of UV irradiation is one minute. We study the surface shape and quality of the moulded gel surface in regards of given cornea irregularity. We study also the intrastromal quality of the cut, with the same cone, with and without the use of the gel.

**Results**
The moulded gel between the cornea and the cone, present an excellent quality of surfaces and a very stable structure. Adheres with the cornea very tight and behave like a new cornea surface. In a model with an induce cornea irregularity, the material reproduces absolute the shape of the irregularity if his surface. The intrastromal femtolaser cut is identical, with the normal cut without the gel.

**Conclusion**
This technique can generate an absolute spherical (or any given shape to the mould) surface of the cornea, and create, based on that an internal custom lentil, correcting all the corneal irregularities, as an ultimate refractive correction, which we call the “custom smile” technique.
Effects of eye motion and active eye tracking on refractive cross-linking

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1. Avedro, Inc.

Purpose
Localization of the cross-linking effect within a sharply-defined XY zone is critical for maximizing anterior curvature change in refractive cross-linking (PiXL). Uncompensated eye motion during CXL and PiXL imparts an uncontrolled and radially asymmetric two-dimensional blur to the UV beam, degrading its spatial localization and making the refractive impact of the treatment uncertain. Active tracking compensates for eye motion by measuring pupil location and repositioning the UV beam in super-real-time. This study provides simulations and ex vivo measurements of PiXL procedures with and without the compensatory action of active eye tracking, based on measured motion profiles from a set of human eyes.

Materials and Methods
Motion profiles were derived from measured pupil trajectories in 130 video recordings of human eyes undergoing screening for CXL. The observed motion of the pupil resulting from a combination of eye and head motion during treatment ranged up to a few millimeters from its mean position. When motion is left uncompensated, blur is imparted to the UV profile. Uncompensated UV profiles were simulated by superimposing a nominal UV beam on the measured pupil trajectories. Compensated UV profiles were simulated in the same way, but included the corrected effects of active eye tracking. Impact on refractive change was simulated using a biomechanical model. Impact was also assessed by applying motion-compensated and uncompensated UV profiles to ex vivo porcine eyes and measuring anterior curvature changes with a Pentacam HR tomography system.

Results
Uncompensated eye motion imparts significant and uncontrolled blur to the UV beam, with nasal-temporal blur being largest. Simulations predict a significant decrease in anterior curvature change if refractive cross-linking (PiXL) is conducted without eye tracking. These findings are consistent with ex vivo measurements in porcine eyes.

Conclusion
Simulations and ex vivo measurements confirm the essential role of active eye tracking in refractive CXL procedures. Refractive changes from PiXL are degraded due to uncompensated, nonuniform eye motion when active eye tracking is not provided in the CXL system, implying that passive eye tracking is insufficient for these procedures.
**Femtosecond laser induced corneal cross-linking towards correction of refractive errors – a parametric study**

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1. Columbia University

**Purpose**
This study aims to further understanding of the nature of interaction between femtosecond oscillator and collagenous tissues, applied onto clinically relevant ophthalmic problems. Our group has recently reported that when femtosecond lasing is restricted to a regime below the optical breakdown threshold, the low-density plasma forms in the vicinity of the focal volume, which in turn enables cross-linking of corneal tissue without photosensitizers. Such a treatment has been utilized to adjust eye refractive power.

**Materials and Methods**
We propose a novel design of the femtosecond laser-based cross-linking system that is capable of treating an eye within clinically relevant timeframe, without sacrificing accuracy and efficiency. Laser pulses are delivered via fiber-optics, and spatially resolved treatment realized with a high-speed, 6-degrees-of-freedom motion system. A parametric study has been conducted on porcine eyes *ex vivo* to investigate efficacy and resolution of the proposed system.

**Results**
Previously reported experimental protocol for treatment of porcine eyes *ex vivo* was repeated on newly developed prototype. The same refractive power adjustment was observed, with a treatment time reduced from 40 to 5 minutes. Further, porcine isolated eyes were tested in a single-factorial experimental design to investigate resolution of the system. Preliminary data have shown that we can adjust refractive power of the eye with approximately 0.75 diopter resolution. Varying lasing and/or other parameters is likely to further increase the resolution.

**Conclusion**
Ultrafast laser-based corneal cross-linking is emerging as an attractive choice due to absence of photosensitizers, and no need for epithelial debriding. Although the underlying physical phenomenon is now understood and described, a rigorous and detailed parametric study is needed to investigate true potential of the proposed method. Furthermore, it is necessary to couple such a study with development of pre-clinical and clinical tools capable of delivering the laser beam safely, and within reasonable timeframe.
Photorefractive keratectomy in patients with primary keratoconus after corneal cross-linking

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Purpose

to evaluate the results of photorefractive keratectomy (PRK) in patients with primary keratoconus after previously performed corneal cross-linking (CXL)

Materials and Methods

The study included 22 patients (22 eyes) with primary keratoconus stage I-II. Corneal cross-linking was performed by standard method. The average sphero equivalent of refraction before PRK was \(-4.58\pm 3.27\) D. Best corrected visual acuity was \(0.9\pm0.2\). Inclusion criteria were a minimum corneal thickness of 450 \(\mu m\) and a stable state of refraction and visual acuity for 1.5 years after CXL. Correction was performed with the excimer laser "MEL-80". The correction results were evaluated in 2 years after PRK.

Results

The majority of patients (19 patients, 19 eyes) achieved uncorrected visual acuity of 0.5 and above (an average of \(0.7\pm0.2\)). This allowed them to dispense with glasses or contact lenses. The result remained the entire time of observation. Nevertheless, in 3 patients (3 eyes) the mean spherical equivalent of refraction decreased by \(-0.23\pm0.18\) D \((p<0.05)\), which was accompanied by a decrease in the uncorrected visual acuity to \(0.3\pm0.1\) and in worsening of keratotopography results.

Conclusion

PRK is a safe method to correct residual ametropia 1.5 years after CXL in patients with primary keratoconus and gives a good functional result.
To evaluate the effect of a novel radial corneal inlay implant (Corneal Arches) in the keratoconic eye.

Mr. Marwan Ghabra, Dr. Hakam Ghabra
I. MAG Optics

Purpose
To evaluate the effect of a novel radial corneal inlay implant (Corneal Arches) in keratoconus.

Materials and Methods
This prospective study included 15 keratoconic eyes. Inclusion criteria were stable refraction for 1 year pre-implantation and 400 µm minimum corneal thickness. Pre-implantation UCVA and BCVA were measured for distance and near. Subjective refraction was taken along with Pentacam scans and contrast sensitivity. Manual radial intracorneal tunnel creation was used by 1 surgeon in all eyes. Determination of the implant location was based on the corneal topography, and identification of the number of implants needed was based on the degree of desired correction. Same measurements were taken postoperatively at months 1, 3, 6 and 12. Follow-up examination also included both corneal IVCM and OCT.

Results
Patients' age ranged from 16 years to 41 years. Seven right and 8 left eyes were operated. Number of implants used ranged from 1 to 2 arches. Visual acuity improved in 13 eyes while 2 remained the same at 12 months follow up. No complications were reported in any of the procedures performed.

Conclusion
Corneal arches are novel corneal inlays which can provide improvement in both unaided and corrected visual acuity in patients with keratoconus.
Topo-guided Removal of Epithelium in Keratoconus (TREK) and accelerated cross-linking – novel tissue sparing customised treatment of keratoconic eyes

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Purpose
To assess the visual, topographic and aberrometric outcomes of a novel tissue saving customized surgical approach for keratoconus (KC) combined with cross-linking (CXL).

Materials and Methods
A prospective, interventional, non-randomized, longitudinal study in a tertiary eye care centre in south India. Epithelial thickness was measured in 50 KC eyes using optical coherence tomography (Optovue Inc, Fremont, CA).

A customised elliptical ablation pattern was planned, which was centred at the location of the steepest point on the anterior tangential curvature map.

PTK-CAM module of the Schwind-Sirius topographer (SCHWIND eye-tech-solutions GmbH, Germany) was used. Theoretical total ablation (epithelium plus stroma) was limited to 75 μm. This was followed by manual removal of surrounding epithelium over the central 8 mm area and accelerated CXL (0.1% riboflavin for 20 mins and UV-A irradiation 9mW/cm² for 10 minutes).

Eyes were evaluated for visual acuity, keratometric and aberrometric outcomes up to one year post-surgery.

Results
Mean major and minor radius of the ablation zone were 3.56 and 3.11 mm, respectively. Mean distance of center of ablation zone was of 0.88 ± 0.35 mm.

Preoperatively uncorrected and corrected distant vision in LogMAR were 0.74±0.05 and 0.24 ±0.03, respectively. Postoperatively these improved to 0.46 ±0.05 (p=0.001) and 0.15± 0.03 (p=0.01) at one year.

Only 2.27% of eyes lost 1 Snellen line on UDVA (uncorrected distance visual acuity) and CDVA (corrected distance visual acuity). On UDVA and CDVA 25% and 54.55% of eyes had no change in Snellen lines, at the same time 54.55% and 18.18% eyes gained 2 Snellen lines or more respectively.

Postoperatively, there was a significant reduction in mean K (2.418 ± 1.211D), defocus (3.65 ± 2.27 μm, 73.7% decrease), spherical aberration (0.690 ± 0.396 μm, 63% decrease), vertical coma (0.562 ± 0.641μm, 29% decrease) and RMS of higher order aberration (HORMS) (0.618 ±0.53μm, 21.6% decrease).

These decreases were greater than previous topo-guided PRK reports with greater tissue ablation.

Conclusion
TREK combined with cross-linking is a safe and effective procedure with “true” customization to the patient needs. It significantly minimized the amount of stromal ablation in KC patients while delivering superior outcomes than topo-guided PRK.
CXL Pre-clinical / Translational
Alcohol cotton bud technique for removal of corneal epithelium at the slit lamp in corneal cross-linking

Dr. Shaheer Ballim
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Purpose
The aim of the study is to describe the process and patient outcomes of a novel technique for the removal of corneal epithelium in the context of epithelium-off corneal cross-linking.

Materials and Methods
This is an observational descriptive case series of all patients who underwent epithelium-off corneal cross-linking for keratoconus using the new technique to remove the corneal epithelium at the study site (Private Ophthalmology Clinic, Durban, South Africa) from January 2017 to July 2018.

The clinical records of all patients who meet the inclusion criteria will be included in the study.

A data extraction sheet is used to extract the relevant demographic and clinical data, keratometry, rate of epithelial healing, degree of corneal haze and incidence of any complications.

Descriptive statistical analysis (proportions, mean and medians) will be conducted.

A brief summary of the technique: The corneal epithelium was removed at the slit lamp under topical anaesthesia. A cotton bud dampened in 70% alcohol facilitated easy and non-traumatic removal of the epithelium in a 8-9mm diameter for subsequent corneal cross-linking.

Results
37 eyes of 26 patients had corneal cross-linking with removal of epithelium using this technique.

Removal of the epithelium was done at a slit lamp in an outpatient office setting.

All patients found the procedure acceptable in terms of patient experience and comfort. Visual results, rate of epithelial healing and rate of complications were comparable with other studies.

There was no evidence of corneal or conjunctival chemical burns within the context of healing after corneal cross-linking. The technique used minimal resources and time. The procedure did not inhibit the effect of corneal cross-linking for keratoconus.

Conclusion
This novel technique is effective, safe and acceptable to patients; and may have be of practical benefit to surgeons performing outpatient corneal cross-linking for keratoconus. It may be of particular benefit in low-resource settings. Further trials and cost analysis may be prove beneficial.
Changes in tear biomarkers in keratoconus after accelerated cross-linking

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Purpose
The purpose of this work was to analyze the expression of matrix metalloproteinase 9 (MMP-9), calcyclin (S100A6), and cystatin 4 (CST4) in the tears of keratoconus patients and their possible variation after accelerated corneal cross-linking with pulsed ultraviolet light delivery (A-CXL). The correlation between the expression of these proteins and the values of several clinical ocular surface parameters was also examined.

Materials and Methods
This prospective, observational study enrolled 20 patients (24 eyes) with different evolutive grades of keratoconus, scheduled to undergo the A-CXL procedure. Tear samples were analyzed employing customized antibody microarray assays for MMP-9, S100A6, and CST4 proteins. Keratometry readings at the corneal apex (Kmax) and the mean keratometry (SimK) values were obtained to examine the postoperative evolution of corneal topography. The state of the ocular surface was evaluated with the Ocular Surface Disease Index (OSDI) questionnaire, tear osmolarity (OSM) test, Schirmer test (SCH), tear film break-up time (TBUT), tear clearance test (CLR), fluorescein (FLUO) and lissamine green (LG) corneal staining.

Results
Eventually, 18 patients (22 eyes) were studied. The concentration of MMP-9 decreased from 104.5 ± 78.98 ng/ml before the surgery to 48.7 ± 24.20 ng/ml after 12 months of follow-up. The concentration of S100A6 decreased from 350.20 ± 478.08 ng/ml to 55.70 ± 103.62 ng/ml. There were no changes in the CST4 concentration after 12 months of follow-up (2231.05 ± 2863.70 vs. 2139.60 ± 2719.89 ng/ml). Although at the end of the study none of the studied clinical variables showed significant changes compared to the baseline, a good correlation between the biochemical and clinical parameters was observed.

Conclusion
A-CXL promoted a decrease in the concentration of MMP-9 and S100A6 in the tear film. This effect may be related to the restoration of corneal homeostasis and the consequent repair of the tissue damage caused by keratoconus. Moreover, the A-CXL treatment did not produce lasting alterations in the ocular surface, as the values of the evaluated clinical parameters did not change significantly.
Comparison of waveform derived corneal stiffness and stress-strain extensometry derived corneal stiffness using different cross-linking irradiances: a prospective study with air-puff applanation of ex vivo porcine eyes

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Purpose
To assess corneal stiffening of standard (S-CXL) and accelerated (A-CXL) cross-linking protocols by corneal bending stiffness (kc[mean] and kc[linear]) derived from dynamic Scheimpflug-based tonometry (CST) and corneal tensile stiffness (kc[ts]) derived from stress-strain extensometry in ex vivo porcine eyes.

Materials and Methods
Fifty-five fresh enucleated and de-epithelized porcine eyes were soaked in 0.1%-riboflavin-solution including 10% dextran for 10 min. Eyes were separated in four groups. 19 eyes were used as controls. Further, 8, 15 and 9 eyes were cross-linked using CCL Vario (diameter of 11 mm) with S-CXL(3*30), A-CXL(9*10) and A-CXL(18*5), respectively. CST measurements (OCULUS, Wetzlar, Germany) was performed in all eyes. Following, corneal strips were extracted by a double-bladed scalpel (5x14 mm) and used for stress-strain measurements (Minimat, Rheometric Scientific GmbH). Kc[ts] were calculated from force by displacement curve. Kc[mean] and kc[linear] were calculated from blinded raw data of CST.

Results
In CST, biomechanical effects of cross-linking are shown by a significant slower A1 velocity, an increased biomechanical IOP and a decreased peak distance, deflection amplitude, integrated radius and SPA1 (P < 0.05). In terms of stiffness, Kc[mean] and Kc[linear] were significantly increased after CXL procedure. Stiffening in S-CXL(3*30) group was significantly increased by +16.96 ± 17.91 N/m and +15.63 ± 14.75 N/m for Kc[mean] and Kc[linear] (P < 0.001), whereas stiffening in A-CXL(18*5) group was not significantly increased by +4.57 ± 3.29 N/m and 4.59 ± 4.2 N/m (P = 0.134 and P = 0.080), respectively. S-CXL(3*30) was significantly more stiffen than A-CXL(18*5) (P < 0.05). Kc[ts] at 4% strain were significantly higher in S-CXL(3*30) (1514.6 ± 606.2 N/m), A-CXL(9*10) (948.1 ± 214.7 N/m) and A-CXL(18*5) (1176.8) ± 215.4 (N/m) compared to controls (704.3 ± 286.0 N/m) by a factor of 3.3, and 2.6, respectively (P < 0.001).

Conclusion
Several CST parameters and Kc[mean] as well Kc[linear] verify corneal stiffening after CXL on a porcine eye globe. S-CXL seems to be stiffen the cornea stronger, demonstrated by Scheimpflug based tonometry and stress-strain extensometry.
Cross-linking of Kpro corneal carrier donor tissue to prevent keratolysis

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Purpose
To describe the *in vitro* studies and case reports that support cross-linking (CXL) cornea carrier donor tissue for the Kpro, and to describe the study design for an ongoing randomized double-blind placebo control multicenter clinical trial.

Materials and Methods
1. *In vitro* - De-epithelialized donor tissue that was cross-linked was compared to de-epithelialized control tissue (no treatment) to determine the resistance to degradation to collagenase.
2. To review case reports from 10 patients that received a CXL donor tissue melts.
3. To report the study design and updates of an ongoing randomized double-blind placebo control multicenter clinical trial in the United States.

Results
1. Tissue that was cross-linked degraded slower than untreated control tissue (16 vs 8 hours, p<0.001).
2. After 2 years, none of the ten eyes that received CXL donor tissue developed a tissue melt.
3. The randomized double-blind placebo control study includes 16 centers, 13 have IRB approval and 26 patients have been randomized and received study tissues.

Conclusion
A randomized double-blind placebo control study will help us better understand if *ex vivo* cross-linking of corneal donor tissue can help prevent of corneas that are carriers for the Boston Keratoprosthesis.
**In vivo** study of femtosecond laser cross-linking of corneal tissue to correct refractive errors

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**Purpose**
We have recently proposed a novel interaction model between femtosecond laser and collagenous tissues without the use photosensitizers. This interaction results in volumetric cross-linking of the target tissue and was first demonstrated in porcine eyes *ex vivo*. Here, we aim to demonstrate long-term effects of the laser-based cross-linking in animal models *in vivo*, and to investigate the potential of this novel interaction for refractive error correction.

**Materials and Methods**
Rabbit models were used in the study. One eye was treated, and the second used as a control. The treatment protocol identical to one previously reported for *ex vivo* porcine eyes was used. The corneal topography of both, treated and control eyes, were assessed before the treatment, and subsequently 48 hours after the treatment, and regular weekly to monthly intervals to assess stability of induced changes. Confocal laser scanning microscopy was utilized to assess cellular structure and density in corneal stroma and endothelium. Two-photon microscopy was used to assess the size of the crosslinked region. Absence of tissue damage, as well as other adverse effects was confirmed with standard histology.

**Results**
The eye refractive power changes induced by this new cross-linking method remained stable over a relative long-term study. Evaluation of the haematoxylin and eosin (H&E) stained corneal sections obtained two days, one week and three months after the treatment showed no difference between control and treated corneas. No wound or wound healing effects were observed. Furthermore, no signs of thermal damage, such as collagen disorganization, stromal oedema and vacuole formation were seen. Quantitative analysis of keratocytes and endothelial cells, revealed that treated and control eyes had similar cell density. In addition, confocal microscopy has shown no presence of inflammatory cells.

**Conclusion**
Femtosecond laser induced crosslinks can be applied volumetrically, as the cross-linking efficacy remains constant throughout the entire depth of corneal stroma. As such this method has potential for adjust the corneal curvature of an eye, and thus be used for non-invasive vision correction. Our results obtained from treating rabbit models *in vivo* showed no adverse effects of the treatment and the resulting eye refractive power remained stable months after the procedure.
Increased resistance against collagenase digestion of porcine corneas cross-linked by hypo-osmolar and hyper-osmolar formulations of riboflavin/ultraviolet A or WST11/near-infrared light.

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Purpose
Increased keratolytic resistance is believed to be one of the mechanisms of action in arresting keratoconus progression. Furthermore, enzymatic digestion is in part responsible for stromal thinning in infectious keratitis. Corneal cross-linking is known to achieve increased keratolytic resistance. The purpose of this study is to compare corneal enzymatic digestion after RF and WST11 induced CXL, and to compare hypo- and hyper-osmolar formulations.

Materials and Methods
Forty-four porcine corneas were treated ex vivo by either hypo-osmolar (RF and WST11) or hyper-osmolar (RF-D and WST-D) formulations, with paired eyes serving as controls. Corneal buttons were placed in a 0.3% collagenase solution and time until full digestion and dry sample weight after six hours was measured.

Results
All four chromophore formulations induced a highly significant increase in keratolytic resistance, as after six hours all control samples were fully digested whereas all treated samples still remained. Mean dry sample weight measured 1.68±0.6 (n=10), 2.19±0.50 (n=8), 1.48±0.76 (n=11), and 1.54±0.60 (n=9) mg, for RF, RF-D, WST11, and WST-D treated samples respectively. There was no significant difference between chromophores (p=0.102). Addition of Dextran did not influence enzymatic resistance.

Conclusion
Both RF and WST11 based CXL significantly increases keratolytic resistance. This is of interest in arresting progressive keratoconus and the treatment of infectious keratitis. Differences in chromophore formulations and safety profile amongst both techniques may broaden the applicability of chromophore CXL.
Purpose
To assess differences in epithelium thickness (ET) and Bowman’s Layer thickness (BLT) maps in keratoconic eyes and healthy eyes.

Materials and Methods
Forty-seven eyes of 47 patients with keratoconus (KC) and 20 eyes of 20 healthy subjects were included in the study. Epithelium and BL measurements were assessed with a recently introduced custom-designed polarization sensitive (PS)-OCT with a conical scanning optics design. En-face corneal epithelium and BLT-maps with a diameter of 11 mm were computed using a custom software. Characteristics of ET- and BLT-maps were recorded. The mean ET/BLT of 21 subsectors were assessed. Further ratios between different sectors were calculated. To assess the diagnostic power of these parameters receiver operator characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) values.

Results
All keratoconic eyes showed a “doughnut profile” in the corresponding ET-map. In the BLT-maps randomly distributed signs of destruction such as thinning, fragmentation or the complete absence of the BL were observed. Statistically significant differences between keratoconic eyes and healthy eyes were found for the thinnest sector in the ET-map and all sectors of the BLT-map. Highest AUC values were calculated for the thinnest sector in the BLT/ET-map and the ratio between the mean thinnest and the mean thickest sector of the ET-map.

Conclusion
PS-OCT imaging enables the visualisation of significant differences of the corneal epithelium and the Bowman’s Layer in en-face thickness maps covering almost the entire cornea from limbus to limbus. Epithelial thickness and BLT profiles could clearly show their diagnostic importance for the distinguishing of keratoconic eyes and healthy eyes.
Long-term effect of corneal cross-linking on endothelial cell count in patients with keratoconus

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Purpose
To evaluate the corneal endothelium after more than five years of corneal cross-linking in patients with Keratoconus.

Materials and Methods
Specular Microscopy was done for 178 eyes in the study to evaluate the number, shape and changes in the corneal endothelium: They were divided into four groups.

First group: 55 eyes of normal cornea as a control group.
Second group: 36 eyes with keratoconus with no prior corneal cross-linking (CXL).
Third group: 29 eyes of Keratoconus who had CXL <5 years ago.
Fourth group: 58 eyes of Keratoconus who had CXL >5 years ago

Results
The study included a total of 178 eyes of 101 subjects. The first group included 55 eyes with normal corneas. The second group included 36 eyes with keratoconus with no prior CXL. The Third group included 29 eyes with keratoconus who had undergone corneal CXL within 5 years of the time of their enrollment in the study. The Fourth group included 58 eyes with keratoconus who had undergone CXL more than 5 years before the time of their enrollment in the study.

Specular microscopy showed a mean cell density of 2445.5 cell/mm² for the First group, 2519 cell/mm² for the second group, 2397.9 cell/mm² for the third group, and 2778.5 cell/mm² for the Fourth group.

Conclusion
CXL has no effect on the corneal endothelium after more than five years.
Measuring the force exerted during eye rubbing

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Purpose
To determine the force that keratoconus patients exert on their cornea during eye rubbing.

Materials and Methods
28 participants with diagnosed keratoconus were asked to reproduce, on a high-precision balance (KERN EW, KERN & Sohn GmbH), the eye rubbing movement and force they use during eye rubbing. Each measurement was taken in quintuple. The average force exerted and the method of eye rubbing were recorded.

Results
We detected three different types of eye rubbing. Each type showed a different strength average: the finger pulp type (n= 16) showed an average of 3.77 N (minimum 1.08 N, maximum 7.22 N), the finger nail type (n=3) had an average of 2.58 N (minimum 0.90 N, maximum 3.53 N), whereas the knuckle type (n= 9) showed an average of 8.26 N (minimum 1.86 N, maximum 19.02 N).

Conclusion
We detected major variations in the force exerted on the globe during eye rubbing, mainly related to the eye rubbing type. These data will be extended and used as the basis for exerting force on ex vivo porcine corneas in our newly developed "automated eye rubbing" device.
Ocular surface immune trafficking and eye rubbing in keratoconus, and its impact on treatment outcomes

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Purpose
To study the status of ocular surface immune cells, tear inflammatory factors and plasma IgE in keratoconus (KC) patients with eye rubbing, and their influence on cross-linking outcomes.

Materials and Methods
Clinical diagnosed KC patients (n=25, 50 eyes) and controls (healthy subjects, n=15, 30 eyes) were included in the study. KC patients who had history of eye rubbing but no signs of ocular/systemic allergy were included. After detailed slit lamp and topography assessments, ocular surface immune cells and tear fluid were collected. Ocular surface wash was performed using sterile saline and immune cells were stained for cell type specific cell surface markers and phenotyped using a flow cytometer to identify neutrophils, macrophages, Natural Killer cells (NK), Natural Killer T cells (NKT) and gamma delta T cells (gdT). Tears collected by Schirmer’s strips were analyzed for tear IgE and other cytokines by cytometric bead array (multiplex ELISA). Blood samples were collected and analyzed for the levels of plasma IgE.

Results
Significantly (*p<0.05) higher levels of NKT and gdT cells were observed on the ocular surface of KC patients compared to controls. In addition, significantly elevated levels of plasma IgE, tear IgE and IL-13 were observed in KC patients compared to controls. Higher levels of tear IgE were observed with increasing grades of KC with eye rubbing. Increased tear inflammatory factors were found to be negatively associated with cross-linking outcome.

Conclusion
High levels of plasma IgE, tear IgE and its receptor (Fc epsilon receptor) bearing immune cells on the ocular surface of KC suggests their role in eye rubbing, KC pathogenesis, potential novel targets for treatments and need for desensitization prior to ensure optimal cross-linking outcomes.
Safety and efficacy of cross-linking (CXL) of human corneal transplants ex vivo: a pilot study.

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Ms. Christina Hofmann¹, Dr. Stephan Holzer¹, Prof. Gerald Schmidinger¹

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Purpose
To assess efficacy and safety of *ex vivo* corneal cross-linking (CXL) of corneal transplants preserved in storage medium in order to reduce postoperative astigmatism and melting of the graft in future real-life transplantations.

Materials and Methods
Experiments were approved by the Institutional Review Board of the Medical University of Vienna (approval 1587/2013). Human donor corneas (n=10) were either treated with Riboflavin 0.1% + Dextran 20% for 30 minutes followed by 10 minutes of UV-A (9mW/cm²) irradiation or sham-treated (30 minutes of Riboflavin administration, no irradiation). Pachymetry was carried out before and after treatment. Stress/Strain measurements of corneal stripes were performed using a customized uniaxial material tester at strains up to 12%. Endothelial cell densities were determined before and 24 hours after treatment.

Results
Corneas were preserved in storage medium for 10.2±5.0 days. There was no difference in corneal thickness between the two groups investigated (before Riboflavin administration p=0.28, after Riboflavin administration p=0.08). Stress needed for a 10% strain was significantly increased by 34% in the treatment group compared to control (p=0.04). No significant difference in endothelial cell density was found before and after treatment in either of the groups (treatment group p=0.45; sham group p=0.49).

Conclusion
Our data indicate successful *ex vivo* CXL of corneal grafts preserved in storage medium. Preoperative cross-linking of donor grafts is a safe procedure concerning endothelial cell survival and significantly increased corneal rigidity. Clinical use of *ex vivo* crosslinked corneal grafts may represent a promising novel approach for reducing postoperative corneal astigmatism and lowering risk of corneal melting.
Safety of high-dose, transepithelial, accelerated CXL with supplemental oxygen on human and monkey eyes

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Purpose
To evaluate high-dose & high-irradiance, transepithelial cross-linking treatments on cynomolgus monkey eyes and human eyes using a supplemental oxygen delivery system.

Materials and Methods
In vivo animal and human blind eye studies were conducted. In both studies, a two-part transepithelial riboflavin formulation was applied to the intact epithelium. Goggles were used to maintain a ≥90% oxygen atmosphere at the corneal plane. Pulsed (1 sec on:1 sec off) UVA at 365 nm was delivered to the eyes at 30mW/cm². In the monkey study, 3 eyes received a UVA dose of 15 J/cm² and 3 eyes received a 20 J/cm² dose. Adverse event, electroretinogram, specular microscopy and histology findings were collected. In the blind eye study, 3 eyes received a UVA dose of 10 J/cm² and 2 eyes received a 15 J/cm² dose. Adverse event findings, specular microscopy and OCT stromal demarcation line depths, were obtained through 3 months follow-up.

Results
In the blind eye study, adverse events were consistent with findings typically seen after CXL, including punctate keratitis (n=4), ocular inflammation (n=3), and corneal haze (n=3). On average, the ECC change from Baseline to Month 3 was 393 + 457 cell/mm². No overt clinical signs of endothelial decompensation or edema were noted. In the monkey study, adverse events included corneal edema, conjunctival hyperemia, and ocular inflammation, which resolved by the 8th postoperative day. Electroretinogram results revealed slightly decreased scotopic and photopic amplitudes in one eye at day 5, secondary to ocular inflammation, which resolved by day 15. Transient decreases of endothelial cell density were seen centrally in two eyes; there were no treatment-related effects on corneal endothelial cell shape or persistent edema in any of the treated eyes. No treatment-related gross or microscopic histopathology findings were noted.

Conclusion
High-dose, transepithelial, accelerated CXL with supplemental oxygen was well-tolerated in both humans and monkeys.
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