Dr Simon Pot and Professor Dr Farhad Hafezi reflect on cutting edge research that is helping to save sight, through the use of light

Using light to save sight

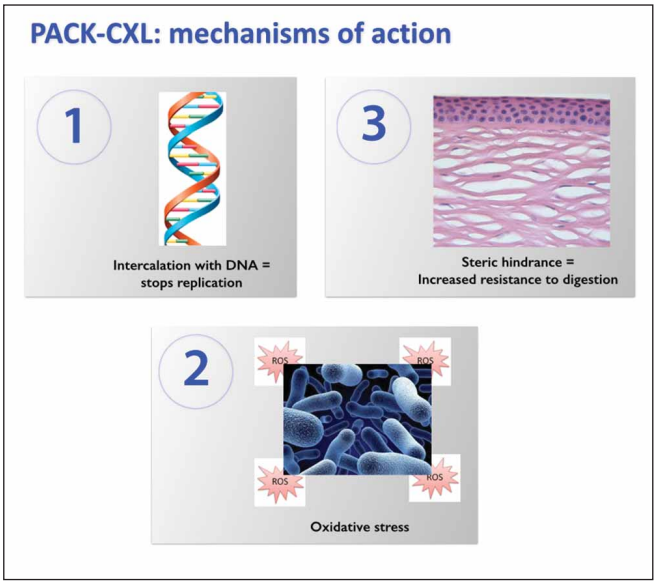
Although modern ophthalmology has seen major advances in the past two decades, a number of challenges still remain. We would like to highlight two of them: keratoconus and corneal infection. Keratoconus (KC) is a progressive, degenerative disease in humans characterised by progressive corneal thinning and impaired biomechanics, leading to reduced vision, and ultimately, legal blindness. KC is a disease of the young, and most often affects children and adolescents with an incidence of 1:500 to 1:2,000 in the general population. Until 2002, there was no cure.

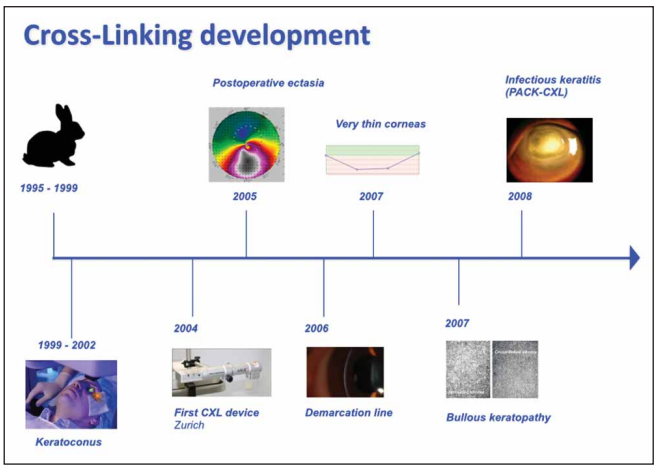
Microbial corneal infection, bacterial and fungal, is a leading cause of global blindness in humans, with an estimated six to eight million new cases every year. Little to no access to medical treatment, and increasing resistance to antibiotics make the treatment challenging from a global perspective. Corneal infection is also a major concern in the veterinary field, affecting >10% of eye patients, mostly cats, dogs, and horses. Here, treatment costs and reduced compliance in the face of an intense topical and systemic treatment often lead to significant loss of vision and even loss of the eye.

The common denominator in these two disease complexes is a new therapeutic technique called CXL, corneal cross-linking with riboflavin and UV-A light. CXL changes the biomechanical characteristics of the cornea, and also has a direct effect on the biology of the tissue. CXL was invented in Dresden, Germany, and further developed in Zürich.

Initial indication: CXL for keratoconus in humans

CXL has been used as a treatment modality in humans since 1999. The technique consists of applying riboflavin (vitamin B2) solution onto the cornea, and then irradiating the tissue with UV-A light at 365nm. Within just a few minutes, the biomechanical strength of the tissue increases by 350%, through the induction of covalent bonds between the amino side chains of the collagen fibres and the proteoglycans of the extracellular matrix. Since its first application, CXL technology has become the standard of care for keratoconus and a number of similar diseases of the cornea in humans. The success rate is more than 95%, and complications are rare, when used correctly. In 2004, the first CXL device was built in Zürich, and for the next four years, the technique was further refined and the spectrum of indications extended.





New indication: PACK-CXL for corneal infection in humans

Photoactivation of riboflavin had been used in photochemical pathogen inactivation technologies (PCT) for fresh-frozen plasma (FFP) for a number of years. This form of photoactivation enabled donor blood to be treated for various pathogens, such as bacteria and viruses, by inactivating them. The same concept is applied in solar disinfection (SODIS), where water is decontaminated by exposure to intense sunlight over several hours, with the addition of riboflavin.

In 2008, we explored the antimicrobial effect of riboflavin photoactivation as a potential application in corneal infection in humans: we conducted a pilot study and treated severe and therapy-resistant infectious melting keratitis. Four of the five patients treated showed rapid improvement. The fifth patient needed several weeks

and continued antibiotic care to improve. We named the new procedure PACK-Crosslinking (photoactivated chromophore for infectious keratitis-crosslinking).

In light of these promising results from our pilot study, Makdoumi proposed a non-randomised clinical study to investigate the efficacy of CXL as a first line therapy for treating bacterial keratitis. A total of 16 patients (13 patients with diagnosed corneal ulcer and three patients with corneal infiltrates) without any prior topical or systematic treatment were treated with standard 3mw/cm^2 CXL as outlined in the original Dresden protocol. Complete epithelial healing occurred in 15 of 16 patients, and all of them responded with symptom improvement and reduced inflammation although two patients needed supplemental antibiotic therapy. This study suggests that not only might CXL be effective in treating advanced ulcerative infectious keratitis as an adjuvant, but also in treating early-stage bacterial infiltrates as a first-line treatment. Most interestingly, the efficacy of killing multiresistant bacteria (MRSA) is more than 98% with the current treatment parameters, making PACK-CXL a tantalising alternative to antibiotic treatment in the light of increasing antibiotic resistance.

PACK-CXL for corneal infection in veterinary patients

PACK-CXL was reported to be successful in >85% of corneal infection/ulcer cases in a compilation of the veterinary literature in which 68 cases were included. Identical results were described in a recent meta-analysis of PACK-CXL-treated human patients in which 104 cases were included. One prospective controlled study examining PACK-CXL treatment efficacy in dogs and cats with corneal ulceration confirmed non-inferiority of PACK-CXL compared to medical treatment and, importantly, a lack of PACK-CXL treatment related complications.

How does PACK-CXL work?

PACK-CXL's antimicrobial therapeutic effect is the result of the effect of UV light interacting with riboflavin as the chromophore. The exact nature of the underlying mechanisms of action is not fully elucidated yet. We speculate that different mechanisms are responsible:

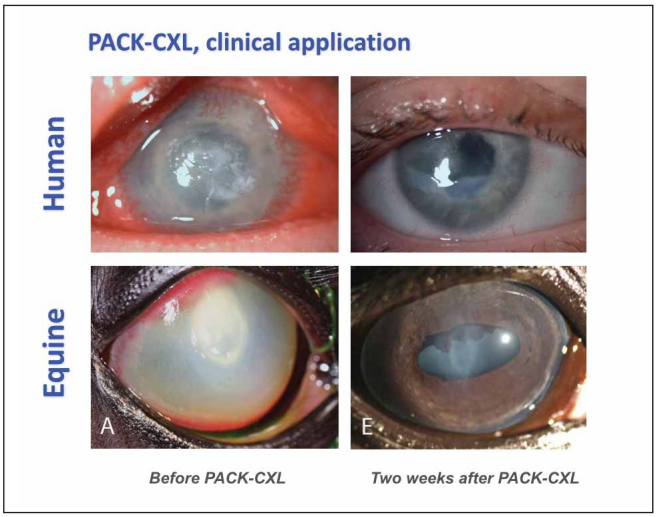
1) Intercalation of photoactivated riboflavin with the DNA and RNA of the pathogen, interrupting replication;

2) Massive amounts of oxidative stress; and

3) Conformational changes in the three-dimensional structure of the collagen, increasing the tissue's resistance to enzymatic digestion during infection.

Outlook

Human application: We aim at establishing PACK-CXL as a rapid and efficient first-line treatment in infectious keratitis. For this purpose, we focus on shortening the treatment time, and increasing efficacy. Also, we aim at miniaturising the technology, and making it mobile, for use in developing countries. Currently, we are conducting a prospective randomised multicentre trial in 14 countries to investigate PACK-CXL as a sole and first-line treatment in human infectious keratitis. This is a non-inferiority study, using the current standard of care (antimicrobial treatment) as control.



Veterinary application: Experimental and clinical studies both show that current PACK-CXL protocols are more effective against bacterial rather than fungal pathogens. Also, a recent study published by our groups described animal species dependency of PACK-CXL penetration depth into the cornea. Therefore, PACK-CXL protocols need adaptation and customisation to target patient and target micro-organism species to optimise treatment efficacy. Also, treatment time shortening will be immensely beneficial to veterinary patients by obviating the need for general anaesthesia. Therefore, a systematic approach to the evaluation of PACK-CXL treatment efficacy and the implementation of PACK-CXL technology in human and veterinary medicine is an important focus of our research. The collaboration between the ELZA Institute, the Ophthalmology Section of the Vetsuisse Faculty and the Laboratory of Ocular Cell Biology at the CABMM is exquisitely suited to answer fundamental scientific and translational lines of questioning involving PACK-CXL.

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