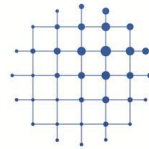




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DELTA-9-TETRAHYDROCANNABINOL (THC) INCREASES CORNEAL WOUND HEALING *EX-VIVO* AND *IN-VIVO*

European Dry Eye Society Congress

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Financial disclosure

M.E. Stern: Employee of ImmunEyez LLC, Irvine, CA, USA

P. Steven, U.Gehlsen, B.Tran: Planing for a patent application

Others: none



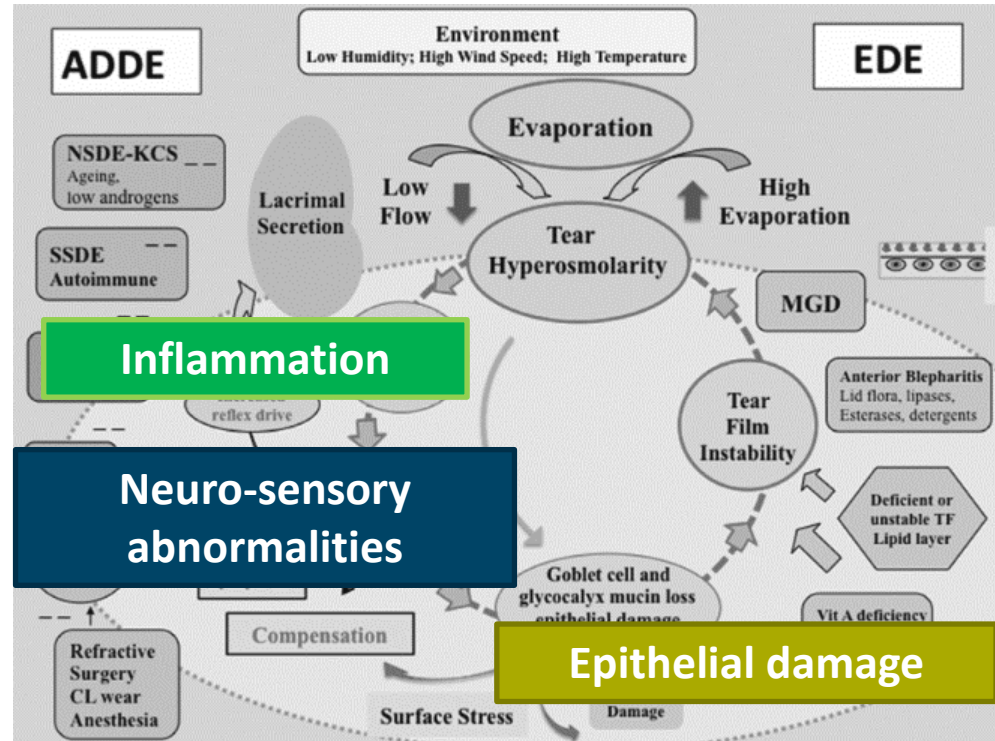
Dry eye disease and endocannabinoid system

Dry eye disease: A multifactorial disease with vicious circle

Endocannabinoid system & Cannabinoid receptor (CBR):

Activation & inhibition of receptors have effects on:

- Inflammation
- Pain and neuro-abnormalities
- Wound healing

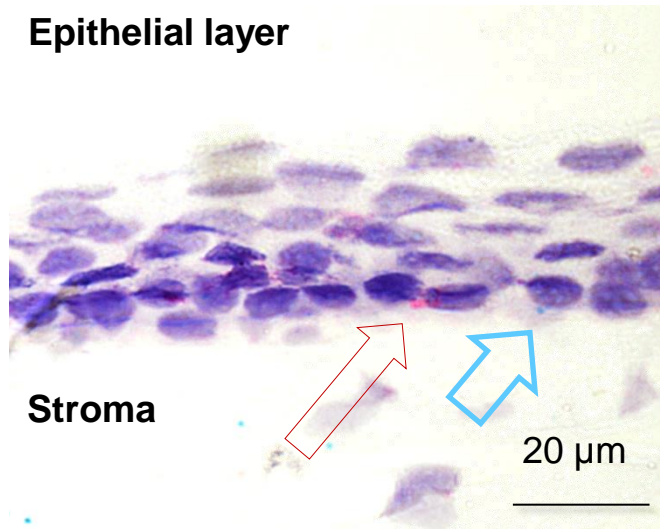


(DEW 2017, adapted from Baudouin et al. 2015)

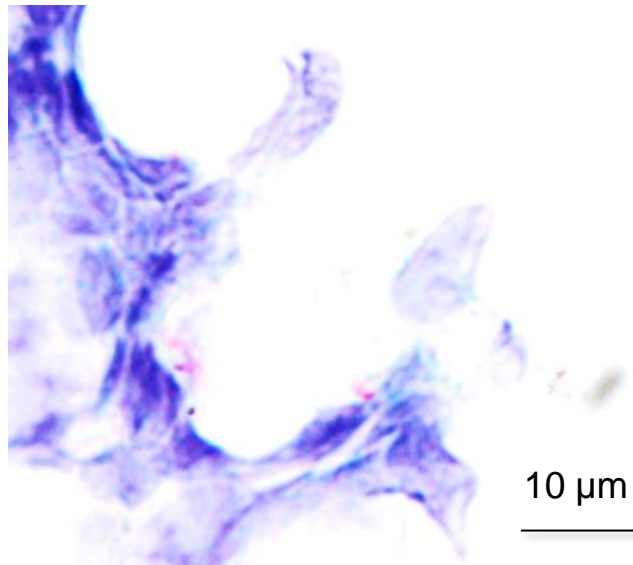
A new eye-drop: Breaking the vicious cycle?

Cannabinoid receptors (CBR) are present at the ocular surface

In-situ hybridization image

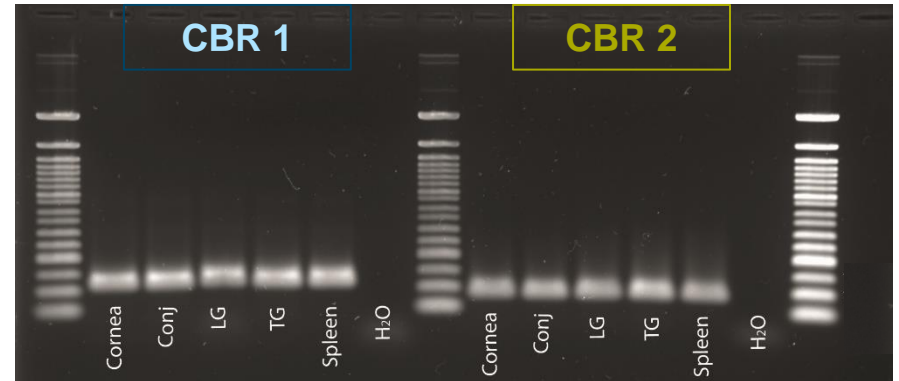


Cornea



Conjunctiva

RT-qPCR results

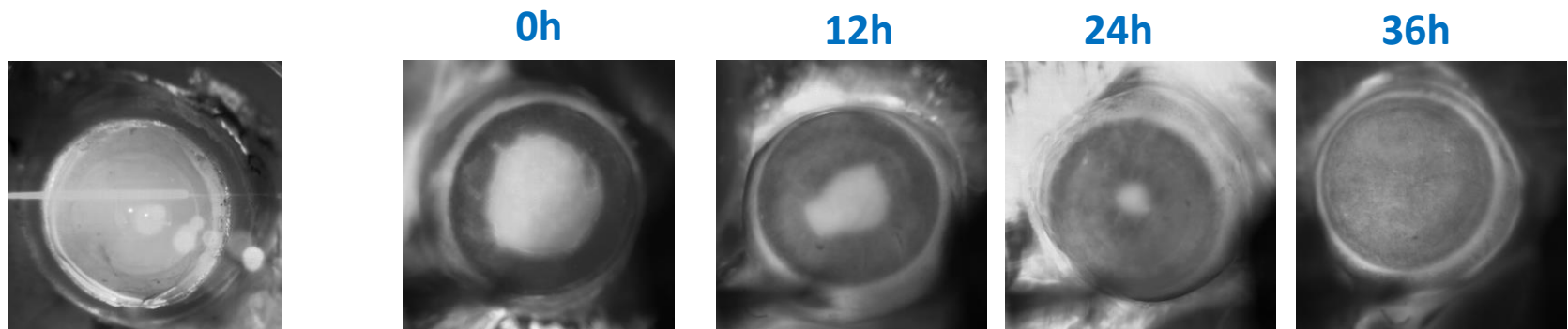


- Cannabinoid receptors (CBR) are present at the ocular surface,
- Using THC (a CBR ligand) to activate the receptors?

Ex-vivo corneal wound healing: Alkali-burned model

Experimental strategy and methods

- Eye-nucleus were excluded from the animal
- Wound induction: Placing a NaOH-soaked filter
- 2 groups (Untreated & treated)
 - Treated: THC (different concentrations) in the culture media (DMEM:F12, penstrops)
 - Untreated: The culture media (without THC)
- Wounds were imaged with fluorescein every 6 hours for 36 hours

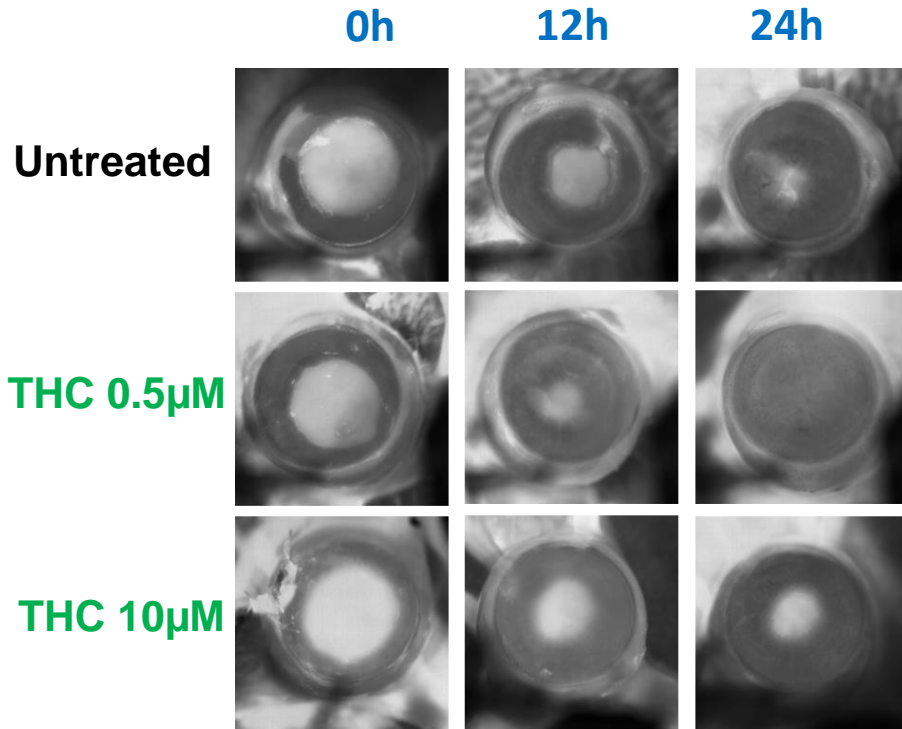


Bright field

(Representative fluorescein images)

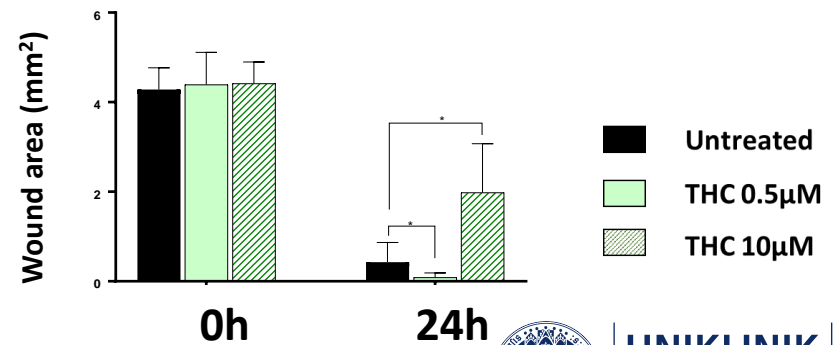
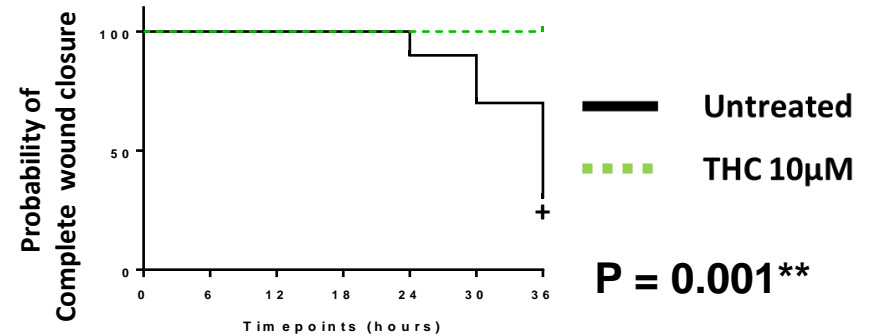
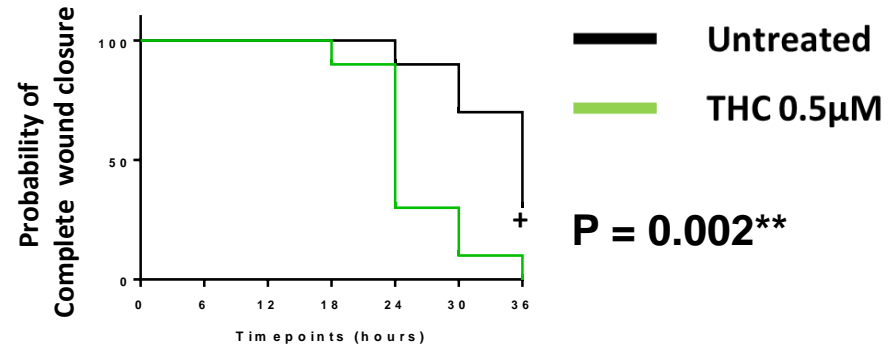


THC Biphasic effect: THC improved the re-epithelialization at 0.5 μ M



(Representative fluorescein images)

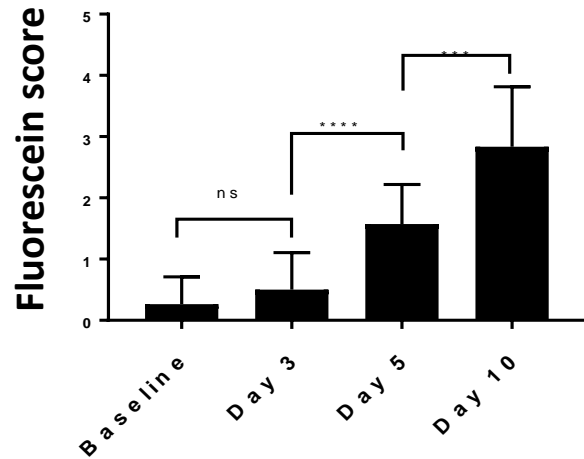
N = 10/ each group



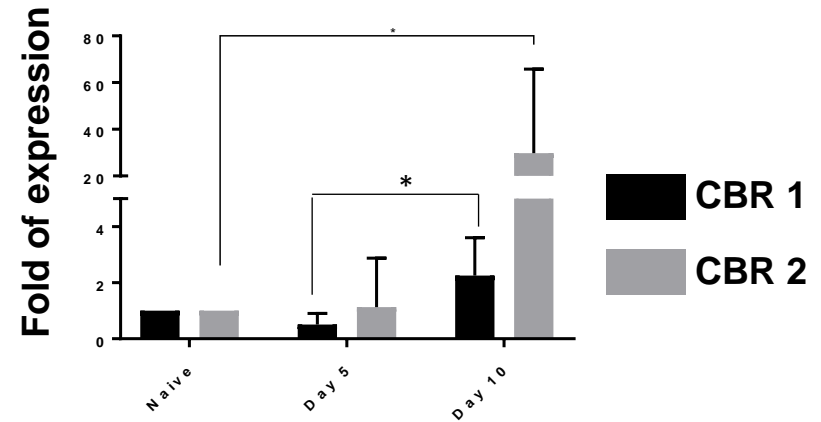
In-vivo desiccating stress model:

Cannabinoid receptor 1 & 2 increased during DED-induction

DED phenotypes

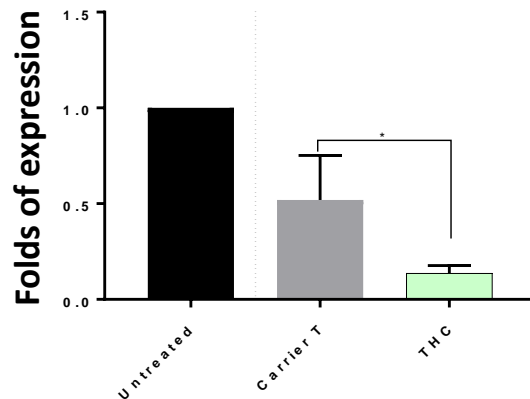


CBR expression in the cornea

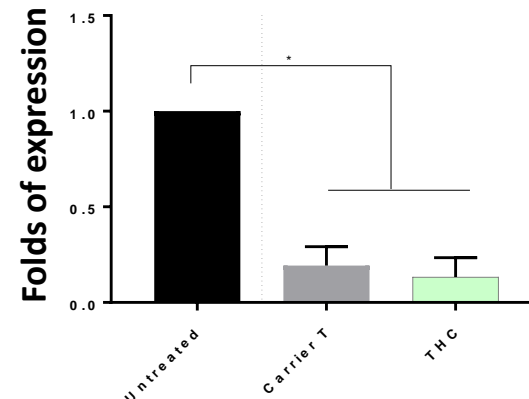


THC treatment reduced CBR expression after 10 days of treatment

CB1 Cornea

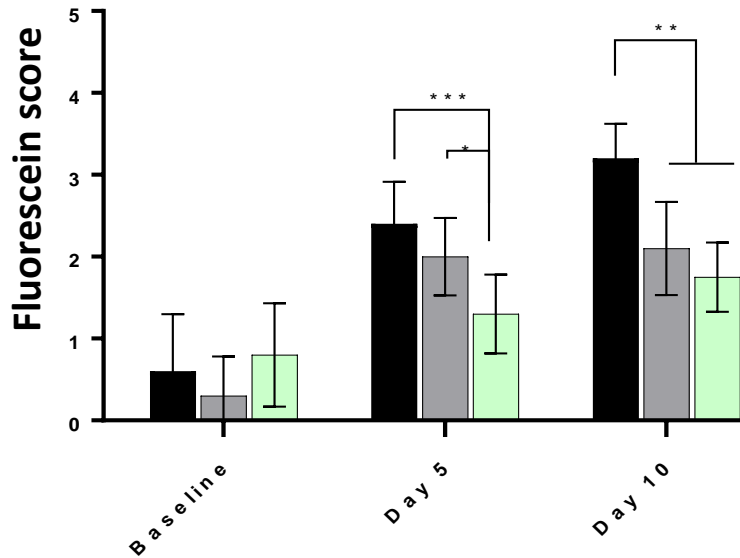


CB2 Cornea

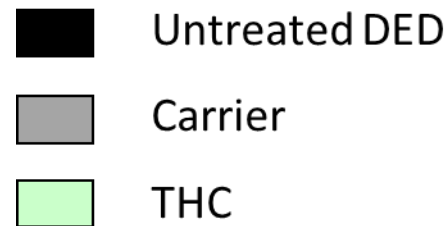
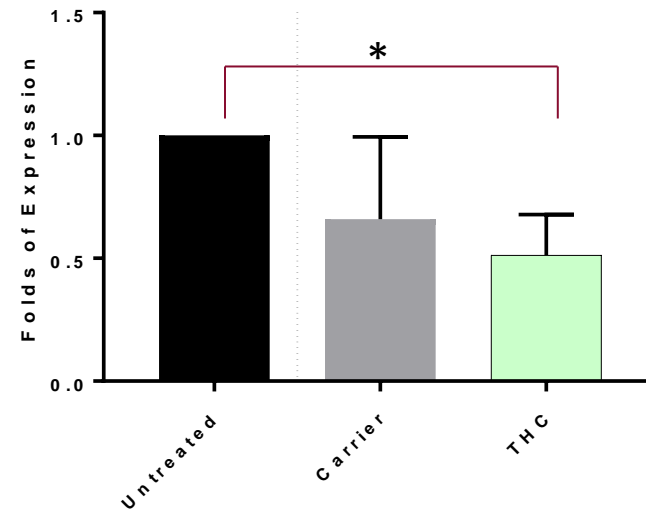


The THC eye-drop reduced corneal epithelial damage and inflammation

Epithelial damage



IL-1 β in cornea



Summary

1. DED animal model and expression of cannabinoid receptors (CBR 1 and 2)

CBR 1 and 2 are present at the ocular surface

CBRs expression increase during the DED

2. Effects of CBR ligands:

Effects of CBR ligands		DED phenotypes and readouts						
		CBRs	FL score	IL-1 β	Cornea sensitivity	Nerve Morphology	Wound healing "Biphasic" effects	
1	THC	↓	↓	↓	Maintained	Maintained	Increase (0.5 μ M)	Delay (10 μ M)

Epithelial damage

Inflammation

Conclusion

The data indicates that THC is a promising candidate for DED

Neuro-sensory abnormalities

THANK YOU FOR YOUR ATTENTION



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