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Dry eye therapy using cannabinoid ligands in a water-free delivery platform

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Summary

Dry Eye Disease (DED) is a high-prevalence and multifactorial disease. A primary goal in DED drug development is to find a multiple-target candidate as well as reduce local & systemic side effects. The endocannabinoid system with its receptors (CB1 and 2) was reported to modulate inflammation, wound healing and pain, which are also DED core pathomechanisms. This project is to confirm the expression and therapeutic functions of ECS on DED induced mouse models.

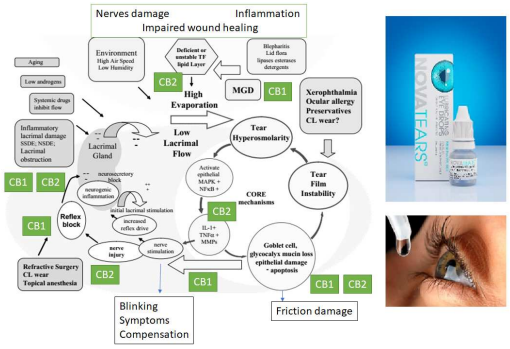
Secondly, highly lipophilic CB ligands are formulated into semi-fluorinated alkanes (SFAs), which are potential carriers with a feature of good tolerability for DED. Thus, an eye drop formulation for CB ligands in SFA will be developed as a promising treatment for DED.

State-of-the-art

The endocannabinoid system (ECS) with its receptors (CB1 and 2) are present in both the ocular surface and the whole body. Previously, stimulating CB was reported to modulate inflammation, wound healing and pain, which are DED core pathomechanisms.

From a drug development point of view, due to the lipophilic properties, aqueous formulations for ECS ligands are unsuitable. Furthermore, surfactants, antioxidants and antimicrobial agents used in aqueous eye-drops were reported to negatively influence DED conditions.

SFAs were introduced as a delivery platform for lipophilic compounds. Furthermore, pure F6H8 is already marketed as artificial tear for DED treatment (EvoTears®, URSAPHARM Arzneimittel GmbH, Germany). SFAs may serve as potential drug-carriers for CB ligands, hereby facilitating superior pharmacokinetics and – dynamics.



Left: Vicious cycle of DED with Cnr expression (adapted from Baudouin et al. 2015), & Right: Novatears® (Novaliq GmbH)

Techniques

Desiccating stress animal model (mouse):

DED phenotype measurement (tear production, cornea integrity & sensitivity), gene expression (RT-qPCR, In-situ hybridization), In-vivo OCT, histology

Drug development:

Techniques for preparing ophthalmic solutions, emulsions, suspensions and sterilization process.

Techniques for characterizing physio-chemical criteria (drug assay, pH, tonicity, viscosity, physical stability).

Techniques for testing drug permeability, tissue distribution

Task description

Confirm the expression and therapeutic function of ECS

- Characterize CB1 and 2 expression at ocular surface and related tissues in naïve and DED-induced mice.
- Characterize ECS functions by activating or inhibiting the CB1 and 2 in the DED-induced mouse model

Develop drug formulations using CB ligands

- Screening drug candidates (CB ligands), selecting composition of SFAs to dissolve the ligands
- Evaluate impact of different formulations on drug efficacy and safety
- Testing novel formulations in the established mouse model

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