Identification of Natural Product Drugs for Corneal Diseases associated with Mutations in the *TGFBI* gene

Ph.D. student: Marina Linova
Supervisor: Henrik Karring
Department of Chemical Engineering,
Biotechnology and Environmental Technology
Faculty of Engineering

Introduction

The cornea is the outermost highly specialized transparent connective tissue of the eyes. It is the eyes' protective shield and has a major role in light refraction.[1] Mutations in the *TGFBI* gene, encoding for TGFBIp protein, is linked to several types of inherited corneal diseases, characterized by the accumulation of insoluble deposits of the TGFBIp protein. The project focuses on two variants of corneal diseases:

- Lattice corneal dystrophies (LCDs) - Caused by A546T mutant FAS 1-4 domain, which destabilizes the TGFBIp protein structure and leads to accumulation of TGFBIp amyloid fibers.(Fig. 1 A)
- Granular corneal dystrophies (GCDs) - Caused by R555W mutant FAS 1-4 domain, which stabilizes the TGFBIp protein and makes it less susceptible to proteolysis. Formation of non-amyloid TGFBIp aggregates are observed.[2](Fig. 1 B)

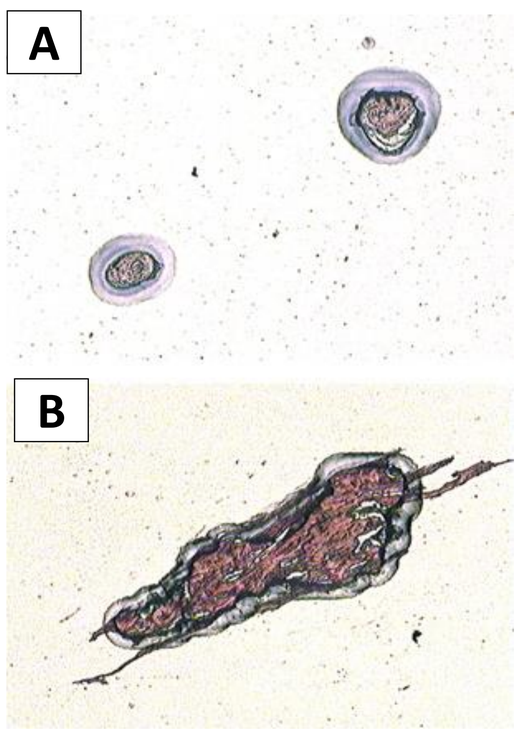

Figure 1. Isolated corneal deposits by laser capture microdissection. **A –** Amyloid deposits from a cornea with LCD, **B –** non-amyloid amorphous deposits from a cornea with GCD. Adapted from Karring et. al.,2012 [2].

Motivation

With the disease progression, the accumulation of TGFBIp can lead to severe visual impairment. At present, the treatment is limited to invasive procedures and, therefore, it is necessary to develop novel less interfering therapies.

Approach

The project explores the possibility of finding natural products, which can bind specifically the mutant forms of TGFBIp protein, but not the wild type of the protein. Compounds stabilizing (LCDs) and destabilizing (GCDs) the TGFBIp protein structure and thus preventing accumulation of misfolded insoluble protein, are the target of the research.

Methods

Production and purification TGFBIp domains – wild type, A546T mutant domain, and R555W mutant domain.

High-throughput screening against natural products and extracts using Bioaffinity Fourier Transform Mass Spectrometry.

Purification of the most promising natural product ligands.

Determination of the stabilizing/destabilizing effect of the pure natural products on the different TGFBIp FAS 1-4 domains.

References:

1. Kolozsvari, L., Nogradi, A., Hopp, B., and Bor, Z. (2002) UV absorbance of the human cornea in the 240- to 400-nm range. *Investig. Ophthalmol. Vis. Sci.* **43,** 2165–2168

2. Karring, H., Runager, K., Thogersen, I. B., Klintworth, G. K., Hojrup, P., & Enghild, J. J. (2012). Composition and proteolytic processing of corneal deposits associated with mutations in the TGFBI gene. *Exp Eye Res, 96*(1), 163-170. doi:10.1016/j.exer.2011.11.014