A brief popular scientific abstract to

Identification of Natural Product Drugs for Corneal Diseases Associated with Mutations in the *TGFBI* Gene

(PhD thesis)

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The cornea is the outermost transparent layer of the eye, having a major contribution to its total focusing power. The cornea is the durable shield of the eye, protecting it from unwanted environmental pollutants and microorganisms, as well as from damaging ultraviolet (UV) light. Because it is a clear transparent tissue, any deposition of abnormal material will greatly compromise its normal functionality and the overall quality of vision. A group of visual conditions, named corneal dystrophies (CDs), are characterized by the accumulation of aberrant deposits in the eye and leading to visual impairment.

Transforming growth factor beta-induced protein (TGFBIp) is a major protein in the cornea. Certain mutations in the protein can destabilize/stabilize its normal three-dimensional structure and cause the formation of deposits with distinct appearances (lattice amyloid-like, granular non-amyloid or a combination of both). Currently, there are no drugs for TGFBIp-associated CDs. Existing treatments are invasive surgical procedures with high reoccurrence rate.

Here, I have explored the possibility to find small molecules isolated from natural product sources, which can bind to the protein and support its proper conformation, hence circumvent its accumulation. Two mutant variants and the wild type protein were included in the research. One of the mutant variants (A546T) destabilizes the conformation of the protein and causes the formation amyloid deposits, whereas the second one (R555W) stabilizes the structure and associate into granular, crystalloid material. The experimental work was performed on recombinantly produced in bacteria protein targets, which were isolated and obtain in a very pure form (above 95 %). From a library comprising 1782 small molecules, 23 were found to bind and form complexes with the protein targets, after a bioaffinity mass spectrometry screening was carried out. To further investigate how the novel small-molecule binders influence the stability of the pathogenic TGFBIp variants, biochemical assays were performed. Two potent small molecules were found for the destabilized A546T mutant variant, and one compound was potentially modulating the stability of the R555W.