00072 Structure Based Drug Discovery Approaches for TGFBI Associated Corneal Dystrophy

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Aims: Corneal Dystrophies (CDs) are a group of bilateral, symmetrical and heterogeneous inherited disorders leading to loss of corneal transparency. The disease is characterised by deposition of aggregated proteins as amyloid fibres, amorphous powder or a mixed form of both in various layers of cornea. Mutations occurring in transforming growth factor beta induced (TGFBI) gene have been found to be the major cause of stromal CDs. Our aims were to understand the disease mechanism better and identify a treatment option that could either prevent/delay TGFBI-Corneal Dystrophy.

Methodology: We have used different methods for different aims. We used a proteomics based LC-MS/MS based approach to understand more about the composition of the protein deposits in the cornea of Dystrophic patients. We have also used various biophysical tools and methods like Circular Dichroism, ThT assays, Transmission Electron Microscopy (TEM), Nuclear Magnetic Resonance (NMR) and Cell toxicity assays to study in-vitro aggregation pattern of the peptides. We have used a combination of in-silico approaches, Weak Affinity Chromatography and NMR to identify and validate our lead compounds that could alter proteolytic processing of TGFBIp.

Result: We identified the protein composition of the corneal deposits from Dystrophic patients and found that TGFBIp, other amyloidogenic proteins and non-fibrillar amyloid associated proteins to be the major components. The proteolytic processing of the control protein was different from the mutant proteins and certain tryptic peptides were abundant in the patients. We also identified model peptides that were highly amyloidogenic and conditions for in-vitro aggregation for these model peptides.

Conclusion: We identified 3 lead compounds that alter the proteolytic processing of the mutant peptide and delay/prevent aggregation of mutant peptides.