NANYANG TECHNOLOGICAL UNIVERSITY

School of Biological Sciences

Reg. No. 200604393R

Research Theme: Structural Biology and Drug Discovery

PhD Research Project Title: Structural basis of amyloid seeds disaggregation by neuroprotective chaperones as a novel therapeutic avenue in TGFBIp-related corneal dystrophies

Principal Investigator/Supervisor: Associate Professor Konstantin Pervushin

Co-supervisor/ Collaborator(s) (if any): NA

Corneal dystrophies (CDs) are characterized as a group of bilateral, heterogeneous inherited disorders. The majority of these CDs in the stromal layer of the cornea has been attributed to mutations found on the TGFBI gene coding for a 683-amino acid long transforming growth factor induced protein (TGFBIp) resulting in loss of vision. Though TGFBIp is present in various other tissues, only cornea-specific aggregation is triggered by the occurrence of these mutations. No effective medical treatment is available except corneal transplantation. The aggregation process is initiated and propagated by the seeds, generated as by-products of proteolytic cleavage of TGFBIp. We identified key highly amyloidogenic peptides derived from TGFBIp in the amyloid depositions which can easily aggregate in vitro forming morphologically well-defined amyloids. No amyloids are found in other tissues and the protein deposits are much denser near the central region of the cornea than in the peripheral region more accessible to blood flow. This indicates that specific blood associated factors, probably disaggregating chaperones, may protect other tissues from amyloidosis. We demonstrated that a native highly abundant amyloid beta disaggregating chaperone Lipocalin-type Prostaglandin D synthase, L-PGDS, is capable of preventing aggregation of highly amyloidogenic peptides derived from TGFBIp during its proteolytic clearance in cornea and disaggregate some of the preformed amyloids in a similar fashion to controlling amyloids in AD. In brain LPGDS interacts with monomeric amyloid beta peptides forming AD plaques, thereby inhibiting their spontaneous aggregation. It also binds to the preformed fibrils and disassembles them into smaller oligomers without hydrolysing ATP. Here we propose structural studies of the TGFBIp-derived amyloid seeds formed by key proteolytic products of TGFBIp. Next, we would like to unravel the structural basis of the aggregation inhibition and investigate amyloid disaggregation modulated by LPGDS. These findings shall lead to formulation of a novel therapeutic avenue.

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Please apply at the following:

Application portal:

https://venus.wis.ntu.edu.sg/GOAL/OnlineApplicationModule/frmOnlineApplication.ASPX