Contribution ID: **2** Type: **Oral**

Differentiating the solution structures and dimer-dimer interfacial dynamics of transthyretin stabilized by tolcapone and tafamidis

Human transthyretin (TTR) is a homotetrameric protein that transports thyroxine (T4) and retinol-binding protein (RBP) in the serum and cerebrospinal fluid. Dissociation of the tetramer form of TTR is believed to result in monomer aggregation into the several identified fatal TTR amyloidosis forms. In the past, several synthesized small molecules were developed to bind and stabilize the dimer-dimer interface of the TTR tetramer as a therapeutic strategy, thereby preventing the dissociation of the tetramer and consequent amyloid fibrilliazation. In this study, using small- and wide-angle X-ray scattering (SWAXS) we analyze the solution structures of TTR and TTR bound respectively with the two therapeutic molecules of tolcapone and tafamidis, in solutions containing different urea concentrations. Our results show that when the binding ratio between the small molecule to TTR is two to one, both tolcapone and tafamidis can preserve the tetramer structure of TTR well up to 8 M urea at 37 oC; however, tolcapone exhibits a better-stabilizing effect than tafamidis, when the binding ratio reduces to 1:1. We also probe the changes of the dynamics of the dimer-dimer interface of TTR upon the binding of the small molecules using NMR, to reveal possible differentiations in the binding dynamics of the two small molecules. These results provide hints on developing a cocktail strategy by adding natural compounds, such as curcumin, to reduce the dosage of the chemical compound in the therapy of TTR amyloidosis.

Primary authors: SHIH, Orion (NSRRC); FENG, Yu-Chen; AGRAWAL, Sashank; LIAO, Kuei-Fen; YEH, Yi-Qi; CHANG, Je-Wei; YU, Tsyr-Yan; Prof. JENG, U-Ser

Presenter: Prof. JENG, U-Ser