International Conference on
"Recent Trends in Structural Bioinformatics and Computer Aided Drug Design"
[ICSBCADD'2019]
11th - 13th December, 2019

The Keap-Nrf2 Defense System: A potential therapeutic pathway for the treatment of Parkinson's diseases

Balasundaram Padmanabhan

Department of Biophysics, National Institute of Mental Health and Neuro Sciences,
Hosur Main Road, Bengaluru – 560029
E-mail: paddy@nimhans.ac.in

Neurodegenerative diseases (ND) include Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. Oxidative damage/stress has been implicated in the pathogenesis of ND. The Keap1-Nrf2 system plays a central role in the protection of cells against oxidative and xenobiotic stress. The Nrf2 transcription function and its degradation by the proteasomal pathway (Keap1-Nrf2-Cul3-Roc1 complex) are regulated by the cytoplasmic repressor protein, Keap1. The Keap1 protein comprises BTB, BACK (IVR region) and Kelch domains. The BTB domain of Keap1 is important for Keap1 homo-dimerization besides its role in Nrf2 degradation via interacting with Cullin-3. The Kelch (β-propeller) domain of Keap1 directly interacts with the Nrf2 transcription factor and negatively regulates its transcription function. The disruption of Keap1-Nrf2 associations is essential to allow free-Nrf2 nuclear export and transcribe antioxidative proteins, like HO-1, NQO-1, etc. which help in curbing the ROS plasma concentration levels through the ARE pathway. The Keap1 protein is a well-established therapeutic drug target for the treatment of ND.

By rational structure-based approach, we have identified new small molecules against the BTB domain and the β-propeller domain of Keap1. We present here the screening process of obtaining hits from computational to crystal structure studies to biochemical studies.