Development of novel strategy for Alzheimer disease therapy based on modulation of molecular chaperone networks

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Sweden

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Development of novel strategy for Alzheimer disease therapy based on modulation of molecular chaperone networks

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Research Abstract

Alzheimer disease (AD) is the most common form of dementia in elderly and costs the society more than cancer and cardiovascular disorders taken together. Unfortunately, at present only symptomatic treatment of AD is available. There is a very high demand on identification of novel targeting mechanisms and therapeutic concepts in AD. The proposed project provides an opportunity to explore novel therapeutic concept based on regulation of protein aggregation

which is considered to be a core of AD pathogenesis. The concept is based on regulation of function of molecular chaperones, proteins that are primarily responsible for maintenance of intracellular protein homeostasis including protein folding and degradation. The action of molecular chaperones Hsp70/Hsp90 is mediated by the co-chaperones, proteins interacting with molecular chaperones and providing specificity of their reactions in the cell. Together they form a highly organized network, responsible for the intracellular protein homeostasis. We aim to regulate the molecular chaperone network by inhibiting the interaction of Hsp70 and/or Hsp90 with particular tetratricopeptide (TPR) motif co-chaperones. Several TPR co-chaperones interacting with Hsp70/Hsp90 were implicated in the pathogenesis of AD. Unique interaction mechanism and small interaction area provide possibility to identify specific inhibitors and regulate metabolism of tau and amyloid beta – two major aggregated species in AD. In the current proposal we will focus on three major objectives: 1. Understanding of complexity of molecular chaperone network in neuronal cells. 2. Identification of novel selective modulators of molecular chaperone network. 3. Validation of molecular chaperone network as drug target using neuronal cell culture and AD animal models. Here using previously developed in our group in vitro assays for protein-protein interactions we will create a comprehensive map of interactions between Hsp70/Hsp90 molecular chaperones with their particular tetratricopeptide (TPR) motif co-chaperones. The obtained results will provide guidelines for the development of novel selective modulators of molecular chaperone network. To identify molecules specifically disrupting particular chaperone co-chaperone interactions we will perform in silico as well as high-throughput screening of compound libraries. Counter screening assays will be performed in order to obtain most selective molecules. These molecules will be used in various cell and animal models AD to validate the role of Hsp70/Hsp90 interactions with the TPR co-chaperones in protein aggregation in the context of AD. The project implementation will be within 3 years. In the first year we will generate a comprehensive map of Hsp70/Hsp90 interactions with all human TPR motif co-chaperones that will include dissociation constants of individual TPR proteins for Hsp70, Hsp90 and their phosphorylated forms. We will also begin compound screening program. During second year we will continue high throughput screening program and initiate hit optimization program to achieve maximal selectivity of identified hits. We will initiate in vivo studies to evaluate compounds mode of action and their effect on protein aggregation. In the third year we will continue and complete in vivo studies using AD mouse model to provide proof of concept for molecular chaperone regulation as novel therapy in AD. Successful realization of the project would extend the current knowledge on protein aggregation in neurodegenerative disorders and could lead to the development of a new class of medicines against AD.

Further information available at:

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