Structure-based Identification and Functional Characterization of SSH1 Inhibitors

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Research Abstract

? DESCRIPTION (provided by applicant): As the major defining characteristic of Alzheimer’s disease (AD) brains is the excessive accumulation of toxic proteins called A? and Tau, understanding the biological mechanisms by which A? connects to tau dysfunction are critical for designing effective therapeutic treatments for AD. We have identified SSH1, a phosphatase

that activates Cofilin, as a promising therapeutic target for AD, as SSH1 impacts both A? and Tau. We have also identified several SSH1 inhibitor compounds that effectively decrease both A?-induced neurotoxicity and Tau hyperphosphorylation while decreasing A? production. In the proposal, we will perform chemical modifications of SSH1 inhibitor compounds to verify the functional groups critical for SSH1 inhibition and establish a platform for lead optimization. We will optimize and carry out in vitro phosphatase activity assays for SSH1 and other dual specificity phosphatases. We will also perform AD-relevant cell-based assays using existing and chemically modified compounds. Complex X-ray crystal structures will be determined using existing and modified compounds in physical contact with the catalytic domain of SSH1, to investigate the molecular basis of their interactions. Double perturbation experiments will be used to probe the contribution of specific inhibitor functional groups and protein residues to ligand binding using modified compounds and site-specific mutagenesis of SSH1. Based on a revised structural model, virtual docking and structure-based design will be performed to improve existing ligand efficiency, and new virtual screening will be carried out to identify additional SSH1 inhibitor chemotypes. Finally, based on the new structure-based ligand efficiency model, we will perform synthesis of a modified compound to demonstrate the proof-of-concept that such modified compound exhibits improved SSH1 inhibitory activity and ADME characteristics in vitro. Therefore, results of this R21 proposal are expected to yield valuable structure function relationship between SSH1 and existing and new compounds as well as establish a structure-based platform for extensive lead optimization and pharmacokinetic studies in a future R01 proposal.

Further information available at:

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