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Identification of small molecular compounds that are useful to suppress mHTT expression, the cause of human Huntington's disease

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Huntington's disease (HD), an inherited neurodegenerative disorder, is caused by aberrant expansion of CAG tri-nucleotide repeats in huntingtin (*HTT*) gene, which results in a production of mutant proteins that are detrimental to neurons. HD clinical symptoms include motor, cognitive and psychiatric disturbances, and patients usually die 10-15 years after the onset of disease. The behavior deficits and neuronal loss can be alleviated by lowering mutant HTT (mHTT) expression in a variety of model systems, suggesting mHTT is causative for genesis and progression of disease and also a target for therapeutic intervention. Despite mHTT is deleterious to neurons, the normal wild-type HTT has a neural protective role. As a result, allele-specific reduction of mHTT is a relatively favorable approach for HD treatment. Supt4h, forming a heterodimer complex with Supt5h, is a transcription elongation factor that aids RNA polymerase II during the process of transcription elongation. Earlier studies we demonstrated that disturbance of Supt4h/5h complex by lowering Supt4h protein levels results in a substantial decrease of transcript production from mHTT allele while leaving wild-type HTT allele affected marginally. We further demonstrated that the motor function deficits of HD transgenic mice are ameliorated by Supt4h genetic knockout and that the life-span of HD mice is prolonged accordingly, suggesting Supt4h is applicable for targeting against mHTT expression and HD. Here, we designed a novel assay platform to screen small molecule compounds that are capable to interfere with the complex formation of Supt4h/5h. Among more than 200 thousands compounds tested, we identified and validated multiple hits with the nature of suppressing mHTT in mouse striatal neural cells or lymphoblastoid cells derived from HD patients. These compounds also showed a rescue effect on rough eye and declined eclosion rate that are caused by mutant HTT in HD-*Drosophila* models, supportive of their potential use in HD.

Biography

Yun-yun Wu is interested in drug development, and glad to have the opportunity to involve from the beginning of the process. She got master degree in learning cell-based experiment from Institution of Biochemistry and molecule biology in National Yang-Ming University. Now she is studying PhD program to find hit and lead compound for ameliorating Huntington's disease progressing.

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