**SIRT1 delays onset and slows disease progression in the N171-82Q** **HD mouse model**

***Mali Jiang 1, Lan Xiang1, Qi Peng1, Zhipeng Hou 2, Jinrong Fu1, Yong Cheng 1, Jiawei Wang 1, Katherine Sommers1, Jin Jing1, Kellie Tamashiro3, Susan Aja 3,4, Bronwen Martin8, Stuart Maudsley9, Tim West 5, Jiangyang Zhang2, Susumu Mori2, Timothy Moran 3, Christopher A Ross1,6,7 , David Holtzman5 and Wenzhen Duan1***

1Division of Neurobiology, Department of Psychiatry and behavioral Sciences, 2Department of Radiology, 3Department of Psychiatry and behavioral Sciences, 4Center for Metabolism and Obesity Research, 6 Department of Neurology, 7Neuroscience , Johns Hopkins University School of Medicine, Baltimore, MD 21287. 5Department of Neurology and the Hope Center for Neurological Disorders, Washington University School of Medicine, St Louis, MO 63110. 8Metabolism Unit, NIA, 9Receptor Pharmacology Unit, NIA, 10Laboratory of Neurosciences, NIA, NIH, Baltimore, MD 21224

Huntington's disease (HD) is an inherited neurodegenerative disorder and characterized by motor, cognitive and psychiatric abnormalities. There is no treatment available to delay onset and/or prevent disease progression. Our previous study has shown that calorie restriction (CR) delays the onset and retards the progression of HD-like phenotypes in a HD mouse model. CR upregulates SIRT1 in tissues including brain. SIRT1 is thought to facilitate the prolonged survival and other benefits associate with CR. We performed a series of experiments to determine if overexpression SIRT1 can modify disease progression in the N171-82Q HD mouse model. N171-82Q HD mice were cross-bred with SIRT1 transgenic mice, both transgenes were driven by the mouse prion protein promoter which results in high expression of transgenes in brain. We found that overexpression of SIRT1 significantly delayed onset of motor deficits and slowed progression of motor dysfunction, attenuated body weight loss and improved glucose tolerance in HD mice. Structural MRI studies indicated that SIRT1 overexpression dramatically reduced brain atrophy HD mice. Further mechanistic studies suggest that SIRT1 normalized levels of BDNF and FOXO3a in the N171-82Q HD mice. Our findings suggest that SIRT1 might be a potential therapeutic target for developing treatment for HD.

Support: Hereditary Disease Foundation (WD), NIH NS055942 (WD), CHDI Inc Foundation (WD), NIH NS35902 (DMH), NIA IRP (BM, SM), NS16375 (CAR)