AUTUMN E. RUSSELL, Dept. of Biology and Environmental Science, West Virginia Wesleyan College, Buckhannon, WV, 26201, WERNER J. GELDENHUYS & JASON D. HUBER, Dept. of Neuroscience & Dept. of Basic Pharmaceutical Sciences & WVU Rockefeller Neuroscience Institute, West Virginia University, Morgantown, WV, 26505, DOMINICK CICALA, MARYAM MAGHAREH, A.S.M. ROKUNZZAMAN, RAPTY SARKER, Dept. of Neuroscience & Dept. of Basic Pharmaceutical Sciences, West Virginia University, Morgantown, WV, 26505, & DAYTON P. L. MILLER, West Virginia School of Osteopathic Medicine, Lewisburg, WV, 24901. Neurodegeneration in traumatic brain injury is attenuated by the MitoNEET ligand TT01001.

The outer mitochondrial membrane protein CISD1 (mitoNEET) has emerged as a critical regulator of mitochondrial redox homeostasis and ferroptosis and is implicated in the pathogenesis of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and ischemic stroke. The objective of this study is to evaluate the efficacy of a novel, previously untested CISD1 modulator (TT01001), to reduce ferroptosis-associated markers and attenuate microglial activation in a rat model. We used a controlled cortical impact (CCI) model of traumatic brain injury (TBI) in aged female Sprague-Dawley rats (16-18 months old). We used immunohistological staining techniques to analyze the damaged and sham tissue samples for ferroptosis-associated markers and microglial response. These findings support the therapeutic potential of CISD1-targeted modulation to mitigate ferroptosis and secondary injury cascades following TBI in the aging brain. Our data establish TT01001 as a promising lead compound for age-adapted therapeutic strategies targeting mitochondrial dysfunction after TBI. This research is supported by NIH Grants P20GM103434 to the West Virginia IDeA Network for Biomedical Research Excellence and RO1 NS19998 to WJG and JDH.