Targeting neuroinflammation in vascular cognitive impairment with a novel, CNS-penetrant, small molecule experimental therapeutic

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Background: Vascular cognitive impairment (VCI) is recognized as the second leading cause of dementia behind Alzheimer's disease (AD). Although a distinct clinical entity from AD, VCI has many of the same risk factors. Indeed, the apolipoprotein ε4 allele, considered one of the strongest risk factors for AD, may also be a risk factor in VCI. Furthermore, most AD patients present with some degree of vascular pathology, and cholinesterase inhibitors used to treat AD patients show some efficacy in VCI patients as well. Pathogenic mechanisms responsible for VCI are diverse and overlapping; however, dysregulated inflammatory processes represent a promising therapeutic target given the large role they play in both vascular and AD-type dementias. Our lab has developed a set of novel anti-neuroinflammatory compounds designed to specifically suppress the disease- or injury-induced overproduction of potentially cytotoxic pro-inflammatory cytokines. One such compound, MW151, has already shown efficacy in multiple models of traumatic brain injury and AD. Given the established efficacy of MW151 in models with pathogenic neuroinflammation, the compound may also provide benefit in a model of VCI.

Methods: We will be testing MW151 in the dietary hyperhomocysteinemia (HHcy) mouse model of VCI. A careful analysis of the temporal expression pattern of selected pro-inflammatory cytokines will first be conducted in order to select an appropriate therapeutic window for administration of MW151. Subsequently, a different cohort will receive MW151 treatment or vehicle as determined by the outcome of the initial study. These animals will be tested for inhibition of elevated cytokine levels. If the drug is successful in this preliminary study, a larger cohort of mice will be tested for rescue of cognitive deficits and translatable imaging correlates, including measurement of cerebral hypoperfusion by arterial spin labeling, metabolic changes by magnetic resonance spectroscopy, and microhemorrhages by magnetic resonance imaging.

Significance: Dementia is a leading health problem, the costs of which have already surpassed those of cancer and heart disease in the United States. There is a dearth of treatments for dementia, including the approximately 20% of cases attributable to VCI. MW151 represents a promising treatment approach for dementia of the AD-type, and potentially vascular dementia as well. This project will help define the appropriate therapeutic window and efficacy outcome measures for the eventual movement of MW151 into clinical trials for VCI.