Dysregulated CNS Inflammation after Acute Brain Injury

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A critical mechanism driving neurodegenerative disease progression is dysregulated inflammation in the brain. Neuroinflammatory repair processes are fundamental to CNS homeostasis, but inflammation that is inefficient, excessive, or prolonged can contribute to neurodegeneration. Overproduction of brain proinflammatory cytokines, for example, has been linked to pathology progression in many CNS disorders. In animal models, and in human head injury patients, CNS injury induces a robust increase in brain cytokines in the first several hours to days after insult, which then subsides. There is extensive evidence that this acute cytokine surge is a key contributor to subsequent synaptic and cognitive dysfunction and other neurologic sequelae. This mechanistic linkage, plus the attractive therapeutic time window of hours-to-days post-insult, provide a rational therapeutic target for intervention in the trauma center setting.

We developed a small molecule drug candidate, MW01-6-189WH (hereafter called MW189), that selectively suppresses disease- and injury-induced glial-derived proinflammatory cytokine increases that are associated with exaggerated neuronal injury and degeneration. MW189 reduces disease pathology and functional impairment in animal models of traumatic brain injury (TBI), aneurysmal hemorrhagic injury (ICH, SAH), and Alzheimer's disease. MW189 is proceeding through the drug development process, and is currently in a phase 1b multiple ascending dose clinical trial in healthy human volunteers. The next step in development is a proof-of-concept phase 2a clinical trial with demonstration of mechanism engagement (change in CSF inflammatory cytokines). This will further establish the safety of MW189, and attract potential commercial, philanthropic, or government partners to pursue the more expansive trials required to bring MW189 to the market.

To be more competitive for phase 2a funding, we propose a feasibility study to measure proinflammatory cytokines in human cerebrospinal fluid (CSF). This pilot study, funded by a UK CCTS pilot award, will be to coordinated by a team of basic/translational and clinical investigators. The study will enroll 20 patients with severe TBI or aneurysmal SAH, collect CSF at 5 time points post-injury, and measure levels of 92 inflammation-related proteins in the CSF. The results will document which inflammatory proteins are increased in CSF after acute brain injury, allowing us to focus our measurements in the future phase 2a study to only those that are most relevant to our planned patient population.