

Mechanism-based Inhibitor of Matrix Metalloproteinase-9 Rescues Brain from Focal Cerebral Ischemia-induced Damage and Improve Neurological Outcomes in Mice

Jiankun Cui¹, Chunyang Zhang¹, Rong Hu^{1,2}, Fanjun Meng^{1,3},
Mijoon Lee⁴, Mayland Chang⁴, Shahriar Mobashery⁴, Zezong Gu¹

¹Department of Pathology and Anatomical Sciences, School of Medicine; ²Interdisciplinary Neuroscience Program; University of Missouri, Columbia, MO; ³Beijing Institute of Genomics Center of Proteomics Analysis, Chinese Academy of Sciences, Beijing, China; ⁴Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN.

Stroke is the third leading cause of death in the US and the primary cause of long-term disability. Acute ischemic stroke, the most common form of stroke, is caused by clotting in the cerebral arteries leading to brain oxygen deprivation and cerebral infarction. The events involved in stroke include brain cell injury or death, breakdown of the blood-brain barrier (BBB), edema, and hemorrhage, which are associated with the expression and activation of matrix metalloproteinases (MMPs), particularly MMP-9. In two focal cerebral ischemia paradigms – the filament-induced transient middle cerebral artery occlusion (MCAo) and the embolus-induced permanent MCAo in mice, we examined MMP-9 proteolysis of extracellular matrix (ECM) components and the neuroprotective effects of the highly selective mechanism-based inhibitor of MMP-9, SB-3CT, which is activated by MMP-9 under pathological conditions. We demonstrated that MMP-9 degrades the ECM protein laminin and that this degradation induces neuronal apoptosis in a transient focal cerebral ischemia model in mice. SB-3CT dramatically blocks MMP-9 activity and decreases MMP-9-mediated laminin cleavage, thus rescuing neurons from apoptosis and ameliorating neurobehavioral outcomes. Significant therapeutic activity of SB-3CT is seen up to 6 h after initial brain damage. Moreover, treatment with SB-3CT attenuates brain MMP-9 activity and protects against delayed

neuronal cell death in the embolus-induced permanent MCAo in mice. We conclude that MMP-9 is a highly promising drug target and that SB-3CT has significant therapeutic potential in stroke patients.