# Brain penetrating TNF decoy receptor is therapeutic in acute stroke

July 18, 2012

Tumor necrosis factor (TNF)-alpha is a pro-inflammatory cytokine that leads to neuronal loss in acute ischemic stroke. The biologic TNF inhibitors (TNFI) cannot be developed for the brain, because these large molecule drugs do not cross the blood-brain barrier (BBB). The TNF-alpha decoy receptor was re-engineered as a fusion protein with a BBB molecular Trojan horse (MTH). The MTH is a genetically engineered monoclonal antibody (MAb) against the BBB transferrin receptor (TfR). The TfRMAb crosses the BBB via receptor-mediated transport on the endogenous BBB TfR and carries into brain the fused TNF decoy receptor pharmaceutical. The MTH-decoy receptor fusion protein is a bi-functional IgG fusion protein that retains high affinity (low nM KD) binding for both the BBB TfR and TNF-alpha. Binding to the TfR triggers fusion protein transport across the BBB and binding to TNF-alpha blocks the pro-inflammatory effects of this cytokine in the brain behind the BBB. A single, delayed intravenous (IV) injection of 1 mg/kg of the TfRMAb-decoy receptor fusion protein caused a reduction in stroke volume and neural deficit in mice subjected to a 1-hour occlusion of the middle cerebral artery. Conversely, IV administration of etanercept, which is a TNF-alpha decoy receptor that does not cross the BBB, had no therapeutic effect in stroke. The work is reported in the Journal of Cerebral Blood Flow and Metabolism.