Brain penetrating erythropoietin is therapeutic in stroke

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Erythropoietin (EPO) is a potent neuroprotective agent, which could be developed for treatment of acute stroke. However, EPO does not cross the blood-brain barrier (BBB), and the BBB is intact in the early hours after stroke when neuroprotection is still possible. AGT-115 is a re-engineered form of human EPO that crosses the BBB via receptor-mediated transport. EPO is fused to a genetically engineered monoclonal antibody (MAb) against the human insulin receptor (HIR). The HIRMAb acts as a molecular Trojan horse to ferry the fused EPO across the BBB following intravenous injection. The engineering and validation of the HIRMAb-EPO fusion protein was reported in the 2010 Journal of Pharmacology & Experimental Therapeutics. The HIRMAb-EPO fusion protein was shown to be rapidly transported across the BBB in the Rhesus monkey, and to have a pharmacokinetics profile that reduces EPO biological activity in peripheral tissues. The HIRMAb-EPO fusion protein reduced the stroke volume and neural deficit by 98% following injection into the brain of rats with a permanent middle cerebral artery occlusion (MCAO), as reported in the 2010 Brain Research. In the rat MCAO model, the HIRMAb-EPO fusion protein was injected into the brain, because the HIRMAb part of the fusion protein does not recognize the rat insulin receptor.