ArmaGen re-engineers erythropoietin for brain penetration

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Human erythropoietin (EPO) is a potent neuroprotective agent for multiple brain disorders, including stroke, brain and spinal cord injury, and Parkinson's disease. However, EPO does not cross the blood-brain barrier (BBB). ArmaGen has successfully re-engineered human EPO as an IgG fusion protein that penetrates the primate brain following intravenous (IV) administration. Human EPO is fused to a genetically engineered monoclonal antibody (MAb) to the human insulin receptor (HIR). The HIRMAb acts as a molecular Trojan horse to ferry the EPO across the BBB via transport on the endogenous BBB insulin receptor. The HIRMAb-EPO fusion protein is a dual receptor specific protein with low nM binding constants for both the human EPO receptor and the human insulin receptor. The HIRMAb part of the HIRMAb-EPO fusion protein cross-reacts with the Rhesus monkey insulin receptor. The HIRMAb-EPO fusion protein rapidly penetrates the BBB in vivo in the adult Rhesus monkey following IV administration, whereas EPO alone is not transported across the BBB. The brain uptake of the HIRMAb-EPO fusion protein in the Rhesus monkey is high, 2% injected dose/brain, and comparable to small molecules. The pharmacokinetics (PK) of the HIRMAb-EPO fusion protein differ markely from the PK of EPO, which minimizes any effect of the fusion protein on bone marrow. EPO-driven neuroprotection in brain is now possible with intravenous administration of the HIRMAb-EPO fusion protein at doses that may minimal effects on erthyropoiesis. The work is published in the June, 2010 issue of the Journal of Pharmacology and Experimental Therapeutics.