Brain-penetrating biologic TNF-Inhibitor is therapeutic in Parkinsons disease

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Parkinson's disease (PD) and Alzheimer's disease (AD) are chonic inflammatory conditions of the brain mediated in part by tumor necrosis factor (TNF)-alpha. TNF-alpha action in peripheral tissues is blocked by the biologic TNF-Inhibitors (TNFI), such as adalimumab, infliximab, or etanercept. However, the biologic TNFIs cannot be developed for brain conditions such as PD or AD, because these large molecule drugs do not cross the blood-brain barrier (BBB). AGT-110, the first BBB-penetrating biologic TNFI, was engineered by fusion of the extracellular domain of the Type II human TNF receptor (TNFR) to a genetically engineered monoclonal antibody (MAb) against the human insulin receptor (HIR). The HIRMAb acts as a molecular Trojan horse to ferry the TNFR decoy receptor across the BBB. The HIRMAb-TNFR fusion protein rapidly penetrates the brain of the Rhesus monkey, with a brain uptake of >3% of injected dose, whereas there is no BBB transport of etanercept (2010 Journal of Biotechnology). A mouse-specific fusion protein of the TNFR decoy receptor and a MAb against the mouse transferrin receptor (TfR), designated the cTfRMAb-TNFR fusion protein, is described in the 2011 Drug Metabolism and Disposition. This cTfRMAb-TNFR fusion protein is shown to be neuroprotective in a mouse model of experimental PD following chronic intravenous (IV) treatment. In contrast, chronic IV treatment with etanercept had no therapeutic effect in PD, because etanercept does not cross the BBB. Treatment of mice with experimental PD resulted in an improvement in 3 assays of neuro-behavior, a 130% increase in striatal tyrosine hydroxylase (TH) enzyme activity, and an increase in immunoreactive TH in the striatum. The work is reported in the 2011 Journal of Pharmacology and Experimental Therapeutics. The work shows that the biologic TNFIs can be developed as brain drugs, providing the biologic TNFI is re-engineered as a fusion protein with a BBB molecular Trojan horse.