Brain of Hurler mouse treated with Trojan horse-enzyme fusion protein

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Adult Hurler mice, a model of Type I Mucopolysaccharidosis (MPS), show reduction in lysosomal inclusion bodies in brain after an 8-week course of twice a week intravenous injections of 1 mg/kg of an IgG-lysosomal enzyme fusion protein. The biopharmaceutical is formed by fusion of the mature murine iduronidase (IDUA) lysosomal enzyme to the heavy chain of a chimeric monoclonal antibody (MAb) against the murine transferrin receptor (TfR). The TfRMAb crosses the blood-brain barrier (BBB) via transport on the endogenous TfR, and acts as a molecular Trojan horse to ferry into brain the fused IDUA therapeutic. The TfRMAb-IDUA fusion protein is bi-functional and binds the murine TfR with high affinity (KD=0.67 nM), and has high IDUA enzyme activity (776 units/ug protein). Treatment caused a 73% decrease in brain cell lysosomal inclusion bodies, and also reduced glycosoaminoglycan levels in peripheral tissues. The study shows that the lysosomal inclusion bodies in the brain can be reversed even in aged 6-8 month old Hurler mice with intravenous enzyme replacement therapy, providing the enzyme is re-engineered to cross the BBB with the molecular Trojan horse technology. The study is reported in the 2011 Molecular Pharmaceutics.