ArmaGen engineers brain-penetrating IDS for treatment of the brain in MPS Type II

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Type II Mucopolysaccharidosis (MPS), Hunter's syndrome, is caused by mutations in the gene encoding the lysosomal enzyme iduronate 2-sulfatase (IDS). Most patients with MPS-II have brain pathology, and recombinant IDS does not treat the brain, because IDS does not cross the blood-brain barrier (BBB). Human IDS was re-engineered as an IgG-IDS fusion protein, AGT-182. The IgG part of the fusion protein is a genetically engineered monoclonal antibody (MAb) against the human insulin receptor (HIR). AGT-182 is a bi-functional protein, which both binds the HIR with high affinity (KD <1 nM), and expresses high IDS enzyme activity. The HIRMAb part of the fusion protein acts as a molecular Trojan horse, which carries the fused IDS across the blood-brain barrier and across the neuronal cell membrane via receptor-mediated transport on the endogenous insulin receptor. The HIRMAb-IDS fusion protein (AGT-182) is triaged to the lysosomal compartment in Hunter fibroblasts, and normalizes glycosoaminoglycan levels. The HIRMAb-IDUS fusion protein rapidly penetrates the BBB in the Rhesus monkey following intravenous administration. The work is published in the 2011 Biotechnology & Bioengineering.