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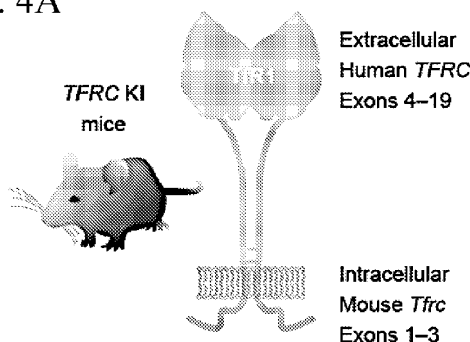
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(54) Title: AAV CAPSID MODIFICATIONS THAT ENABLE IMPROVED CNS-WIDE GENE DELIVERY THROUGH INTER-ACTIONS WITH THE TRANSFERRIN RECEPTOR

FIG. 4A



(57) Abstract: Developing vehicles that efficiently deliver genes throughout the human central nervous system (CNS) will broaden the range of treatable genetic diseases. Applicants engineered an AAV capsid, BI-hTFRL, that binds human Transferrin Receptor (TfRL), a protein expressed on the blood-brain barrier (BBB). BI-hTFRL was actively transported across a human brain endothelial cell layer and, relative to AAV9, provided 40-50 times greater reporter expression in the CNS of human TFRC knock-in mice. The enhanced tropism was CNS-specific and absent in wild type mice. When used to deliver GBA1, mutations of which cause Gaucher disease and are linked to Parkinson's disease, BI-hTFRL substantially increased brain and cerebrospinal fluid glucocerebrosidase activity compared to AAV9.