

**[194] Long-Term Phenotypic Correction of Feline Lysosomal Storage Disease by Intracranial AAV Gene Therapy**

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Deficiency of lysosomal  $\beta$ -galactosidase ( $\beta$ gal) causes storage of GM1 ganglioside, resulting in progressive neurological deterioration and death, often by 5 years of age. AAV gene therapy has been extraordinarily successful in the GM1 mouse model, (*Mol Ther*, 15:30, 2007; *PLoS One*, 5:e13468, 2010), resulting in enhanced survival and complete clearance of storage in the brains of GM1 mice. Because the mouse brain is ~1000 times smaller and much less complex than the human brain, it is important to test AAV gene therapy in an animal model whose brain size and complexity more closely resemble humans. First reported ~40 years ago, the feline GM1 model presents an unparalleled opportunity to evaluate AAV gene therapy in a non-rodent, 'large animal' prior to initiating human clinical trials. In the current study, AAV2/1 or AAV2/rh8 vectors expressing a feline  $\beta$ gal cDNA (3.1-12.0e12 g.c. total) were injected bilaterally into the thalamus and deep cerebellar nuclei of 2-month old GM1 cats (disease onset ~3.5 months). In treated brains collected 4-16 weeks post-injection,  $\beta$ gal was distributed throughout the entire anterior-posterior axis of the cerebrum and cerebellum at levels up to 4 times normal. Cervical and lumbar spinal cord regions demonstrated  $\beta$ gal activity 0.5 -1 times normal, and filipin staining demonstrated extensive clearance of storage material. Little evidence of an inflammatory cellular infiltrate was observed in H&E-stained brain sections, though serum antibody titers to the AAV vectors were pronounced (~1:65,000). Long-term therapeutic experiments in 2-month old GM1 cats were conducted using the same vector dose and route of delivery. Currently, AAV-treated GM1 cats are 16, 14 and 12 months of age, with no evidence of clinical neurological disease (untreated humane endpoint,  $7.7 \pm 0.8$  months, n=9). Treated GM1 cats demonstrate normalization of MRI brain lesions and absence of gait abnormalities typical of untreated cats. Other than serum antibody titers, no evidence of vector toxicity has been documented, and no  $\beta$ gal activity was detected in peripheral blood mononuclear cells. Further encouraging results come from treatments performed nearer to clinical disease onset (3.0 months of age, 2 weeks prior to disease onset), in which 2 GM1 cats remain neurologically normal at 8.3 months of age. These translational studies provide strong support for the initiation of AAV-based clinical trials for human GM1 gangliosidosis.

**Keywords:** AAV Vectors; Neurological Disorders; Genetic Diseases

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