3T MRI and MR spectroscopy of a Feline Model of GM1 Gangliosidosis after AAV-Mediated Gene Therapy

Heather L. Gray-Edwards[1], Nouha Salibi[2], Diane Wilson[1], Ashley Randle[1], Ronald J. Beyers[3], Thomas S. Denney[3], Ravi Seethamraju[2], Shumin Wang[3], Xiaotong Sun[3], Allison M. Bradbury[4], Victoria J McCurdy[4], Aime K. Johnson[5], Nancy Cox[1], and Douglas R. Martin[4]

[1]*Scott-Ritchey Research Center, Auburn University, Auburn, Al, United States,* [2]*MR R&D, Siemens Healthcare, Malvern, PA, United States,* [3]*Department of Electrical and Computer Engineering, Auburn Univeristy, Auburn, AL, United States,* [4]*Anatomy, Physiology and Pharmacology, Auburn University, Auburn, Al, United States,* [5]*Clinical Sciences, Auburn University, Auburn, Al, United States*

Target Audience. Studies outlined in this abstract will benefit those interested in Magnetic Resonance Imaging as an *in vivo* biomarker of neurodegenerative lysosomal storage diseases and AAV-gene therapy.

Purpose. Human GM1 gangliosidosis results from a deficiency of lysosomal β-galactosidase (βgal), which causes storage of GM1 ganglioside, progressive neurodegeneration and early death, often by age five. MRI and MRS were used to non-invasively evaluate the effect of gene therapy in a feline GM1 model, prior to initiating human clinical trials.

Methods. AAV2/rh8 vectors expressing a feline βgal cDNA (3.1-12.0e12 g.c. total) were injected bilaterally into the thalamus and deep cerebellar nuclei (DCN) of 2-month old GM1 cats (disease onset ~3.5 months). MRI and MRS data were acquired on a 3 Tesla MAGNETOM Verio scanner (Siemens Healthcare, Erlangen, Germany) using an 8 channel phased array wrist coil (Invivo corp Gainesville, FL, USA). Anatomical coronal images were acquired using 3D MPRage (magnetization-prepared rapid gradient echo) with 0.4mm isotropic resolution and TR/TE of 1900/3.3ms, followed by 2D axial T2 TSE images with TR/TE of 4630/107ms and a resolution of (0.3x0.3x1)mm^3, Single voxel spectroscopy (SVS) was then acquired using PRESS (Point RESolved Spectroscopy) with CHESS (CHESS (CHEmical Shift Selective) water suppression, TE/TR = 30/2000ms and 32 averages. In all animals a (4x5x13)mm^3 voxel was placed in the parietal cortex that was well defined on the high resolution anatomical images. All metabolite peak integrals were normalized to creatine (Cr). MRI and MRS data were analyzed using EFilm 3.2 software (Merge Healthcare, Chicago) and jMRUI (Java Based Magnetic Resonance user Interface, http://www.mrui.uab.es/mrui/mrui_homePage.shtml.), respectively.

Results.

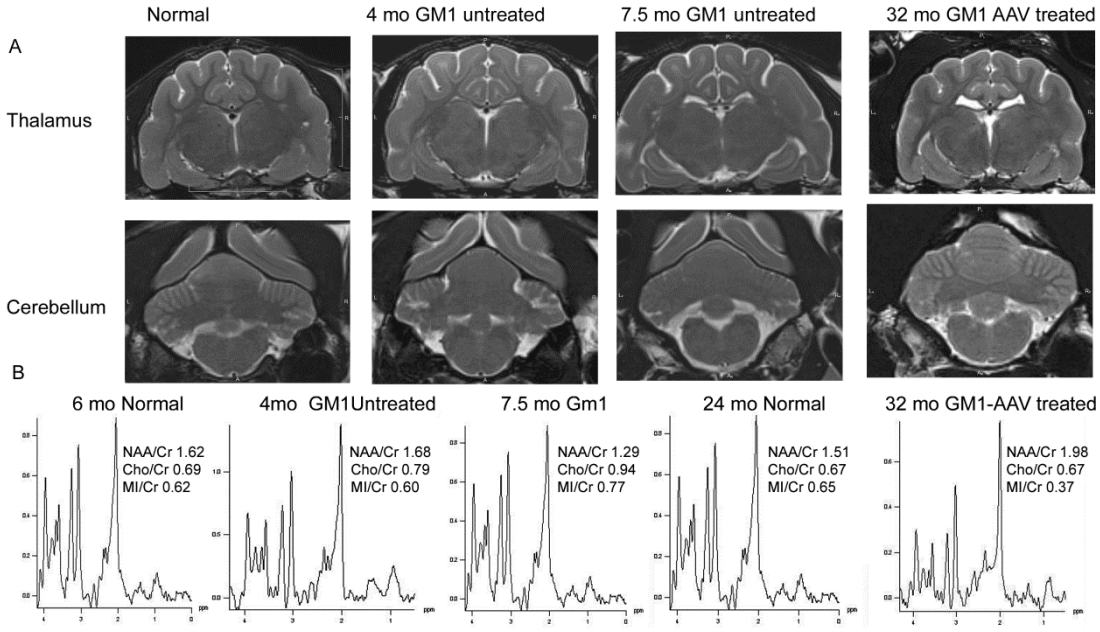

Figure 1. ***3T MRI and MRS of untreated GM1, AAV-treated GM1 and normal cats.*** **A)** T2 images show relative iso- or hyperintensity of the white matter in the untreated GM1 cat compared to gray matter at 4 mo. and complete reversal of gray/white matter relative intensity just prior to humane endpoint (7.5 mo.). At 32 mo. the AAV-treated GM1 cat has normalized gray/white matter intensities. Similarly, the DCN of the AAV-treated GM1 cat are hypointense to the surrounding gray matter as compared to the 7.5 mo. untreated GM1, in which the DCN and gray matter are isointense. **B)** MRS shows decreased ratios of N-acetyl-aspartate (NAA)/Creatine (Cr), increased choline (Cho)/Cr and increased myoinositol (MI)/Cr in the 7.5 mo. old untreated GM1 cat as compared to normal. The AAV-treated GM1 cat showed increased NAA/Cr compared to normal. MI/Cr was also decreased in the AAV-treated GM1 cat. Voxel placement was consistent between cats and located in the occipital cortex.

Discussion and Conclusions. MRI shows preservation of white and grey matter structures after gene therapy that has, in ongoing studies, extended the life of GM1 cats >3 fold with negligible neurologic signs. Data collected in the untreated GM1 cat are consistent with the published literature in humans[1]. Data in the 32 month AAV-treated cat are intriguing and future studies are planned for determination of individual metabolite variations using an external reference solution with the phantom replacement quantification technique [2,3].

References. 1. Erol, I. et al. *Eur J Paediatr Neurol* 2006. 2. Soher, B.J.,et al. *Magn Reson Med* 1996. 3. Michaelis, T. et al. *Radiology* 1993.