3T MRI and MR Spectroscopy of an Ovine Model of Tay-Sachs Disease 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], 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

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. Tay-Sachs disease (TSD) is a form of GM2 gangliosidosis in humans that is untreatable and fatal by 5 years of age. It is caused by a mutation of the α subunit of the dimeric enzyme hexosaminidase (Hex). We performed intracranial (IC) AAV-mediated Hex gene replacement in α subunit deficient Tay-Sachs Disease (TSD) sheep. Global distribution of Hex activity at normal or above normal levels throughout the sheep brain provides support for human clinical trials scheduled to start in 2013. With brain and body size on the same order of magnitude as children, the authentic TSD model in sheep provides invaluable opportunities to develop non-invasive methods to chart disease progression or amelioration in human clinical trials.

Methods. The AAV2rh8 serotype was used to express ovine Hex α and β subunits after injection bilaterally into the thalamus (1.54×10^{12} gc/vector) and left lateral ventricle (4.2×10^{12} gc/vector) of TSD sheep. MRI and MRS data were acquired on a 3 Tesla MAGNETOM Verio scanner (Siemens Healthcare, Erlangen, Germany) at 10-11 months using an channel phased array coil (Siemens Healthcare, Erlangen, Germany). Anatomical coronal images were acquired using 3D MPRage (magnetization-prepared rapid gradient echo) with 0.4mm isotropic resolution and TR/TE of 1900/3.3 ms, 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 (CHEmical Shift Selective) water suppression, TE/TR = 30/2000 ms 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) respectively.

Results.

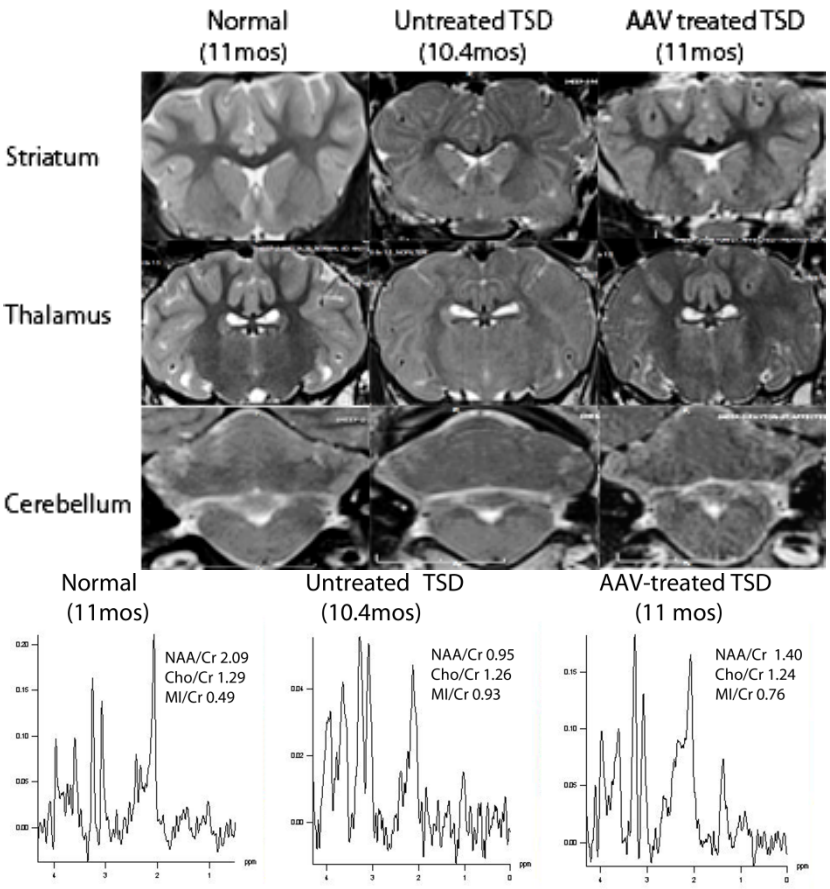

Figure 1 *3T MRI and MRS of normal and TSD sheep brains.* Axial T2 weighted MRIs show that cortical white matter is iso- to hyper-intense compared gray matter at the level of the striatum and thalamus in an untreated TSD Sheep (10.4mos) just prior to humane endpoint. The AAV-treated TSD sheep (11mos) has normalized white:gray matter intensities. MRS shows decreased N-acetyl-aspartate (NAA)/Cr and increased Myoinositol (MI)/Cr in the untreated TSD sheep versus normal. The AAV-treated TSD sheep had NAA/Cr and MI/Cr levels intermediate to normal and untreated, while Choline (Cho)/Cr was decreased. Voxel placement was consistent between sheep and located in the parietal cortex.

Discussion. 3T MRI and MRS images in TSD sheep show preservation of white and gray matter structures and normalization of brain metabolites after gene therapy.

Conclusions. Gene replacement in the ovine model of TSD results in normalization of both brain architecture and metabolites, and results in the untreated TSD sheep are consistent with studies in human patients[1-3]. Future studies are planned for determination of individual metabolite variations using an external reference solution with the phantom replacement quantification technique[4,5].

References: 1. Imamura, A. et. al *Neuropediatrics* 2008. 2. Aydin, K., et al. *Pediatr Radiol* 2005. 3.Assadi, M. *et al. Eur J Pediatr* (2008). Soher, B.J., et al. *Magn Reson Med* 1996. 5. Michaelis, T.et al. *Radiology* 1993.