Lay Summary. April 1st, 2014

TITLE: AAV9-mediated human acid sphingomyelinase expression in nonhuman primate brain: Preclinical development of gene therapy for Niemann-Pick disease type A.

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Correcting non-functional genes in the central nervous system, in some cases, will require global expression of efficacious levels of a corrected version of gene. In infants with Niemann-Pick disease type A (NPDA), an extensive distribution of acid sphingomyelinase (ASM) is required to increase the abnormally low levels of enzyme, and reverse the pathological phenotype.

Adeno-associated virus serotype 9 (AAV9) has risen as a very promising vector to obtain global coverage of the brain when injected into the CSF through the cisterna magna, a very viable surgical technique in infants. Accordingly, AAV9 vector hosting a functional copy of the ASM gene (AAV9-ASM) showed good cortical distribution; however we are not certain of ASM expression levels in the brain. In contrast, high signal of another protein called CCL5, that is up-regulated by ASM over-expression, was present suggesting an increase of ASM in the brain. No adverse effects or signs of neuropathology were seen in these animals.

Recently, two more animals were injected and evaluated at different time points after delivery. No differences were found 30 and 90 days after injections of AAV9-ASM into the CSF with ASM expression level within range of normal levels in the NHP (background).

To investigate ASM expression levels in NHP further, we designed a new AAV9-hASM vector with a synthetic epitope tag that is easily detectable by standard histochemical staining. This data will confirm distribution of the vector in the brain. We also plan to inject the vector into the NPDA mouse model to evaluate bioactivity.

In summary, CSF delivery of AAV9-hASM in NHP appears to be safe for at least 3 months. Based on the lack of neurological effects in NPD-B, where less then 20% ASM is preserved in the brain, we believe that that we do not need to restore ASM levels in the brains on NPD-A children to 100%. Our results up to now suggest that we are probably restoring some ASM levels in NHP brains after CSF delivery of AAV9. However due to normal (100%) background levels of ASM we cannot directly detect ASM after AAV9-hASM administration into the CSF. We hope to demonstrate ASM gene transduction with “tagged” vector.