

Tay-Sachs Gene Therapy Consortium
Progress Update
March 2010

1. The performance of AAV-treated GM2 mice in behavioral tests of motor and neurological functions is comparable to that of age-matched normal mice.
2. In a related project sponsored by Auburn University, University of Massachusetts Medical School and the National Institutes of Health (NIH), a GM1 cat treated by AAV injection is now 6.5 months of age and its behavior continues to be indistinguishable from a normal littermate. Disease onset in this model typically occurs at 3.5-4.0 months of age. Neither the veterinary neurologist that has been following this cat on a regular basis, nor researchers with many years of experience with this cat model are able to identify any signs of disease. A number of AAV-treated GM1 cats are currently in the pipeline.
3. An AAV-treated GM2 kitten is now 2 months of age and continues to do well. By 3.5 months of age we will know better whether the AAV-injections are having an effect since untreated GM2 kittens by this age are capable of standing but not ambulating. By 2-2.5 months of age untreated GM2 kittens usually display whole body tremor. Another GM2 kitten has been treated in late March, 2010.
4. Breeding of the GM2 cat colony continues at an accelerated pace to generate GM2 kittens for therapeutic efficacy experiments.
5. The AAV vectors encoding feline alpha and beta-subunits have been tested in heterozygote (HZ; carriers of one normal and one mutant copy of the gene) GM2 cats and levels of enzyme expression in the brain and cerebellum are up to 60-fold higher than normal at 1 month after injection. Importantly there was no evidence of inflammation.
6. The Tay-Sachs sheep colony has been very productive and we have now identified four affected lambs born in the last two months. Two affected lambs and age-matched controls will be used to characterize in detail disease progression using a battery of tests to assess neurological function.
7. We are currently cloning the sheep alpha and beta genes and will produce AAV vectors carrying these genes for injection into affected lambs.
8. Two affected lambs will be injected with AAV vectors encoding the sheep alpha and beta genes. This experiment is very important to demonstrate the effectiveness of our approach in the only Tay-Sachs disease animal model available that displays a severe phenotype.
9. The retrospective natural history study is in its final phase. The results of this study will be presented at the annual family meeting of the NTSAD. Prospective studies in LOTS patients are currently underway and studies in infants are in preparation. Both aim to develop biomarkers and validate imaging and clinical scoring scales that will be used to assess treatment effects in the clinical trial.