Tay-Sachs Gene Therapy Consortium
Progress Update
December 2010

The TSGT Consortium is on schedule in its NIH-funded program aimed at initiating a human clinical trial in late 2013. Financial support to conduct the clinical trial is presently not secured. The TSGT will continue to pursue its policy of working closely with the patient community/private foundations and will apply for NIH support to conduct the clinical trial.

In the second half of 2010 the TSGT developed a clinical trial plan and recently submitted to the Food and Drug Administration (FDA) an information package summarizing our development program for the Investigational New Drug (IND) application necessary to initiate the clinical trial. A teleconference is scheduled with officials at the FDA in the beginning of February 2011.

As a result of the Natural History study we developed a clinical severity scoring system for Infantile TSD and SD patients. This is critical for the clinical trial. We have designed additional studies to extend and validate this scoring system in Juvenile patients, and also to develop an MRI-based scoring system to describe changes over time in the brain of Infantile and Juvenile TSD patients.

In January 2011 we will submit an application to the NIH Rapid Access to Investigational Drugs (NIH-RAID) program to support manufacture of clinical grade (GMP) AAV vectors for the clinical trial.

Therapeutic Efficacy Experiments in Large Animal Models of GM2-gangliosidoses

Many of the critical therapeutic efficacy experiments in GM2 cats originally scheduled for Year 2 of the NIH-funded project are well ahead of the originally planed timeline. Currently, 9 GM2 cats have been treated with high-dose AAV gene therapy via bilateral injection of the thalamus and cerebellum (brain targets). These cats range in age from 2.3 to 11.4 months, whereas untreated GM2 cats live to only 4.5 months. The four oldest cats treated by high-dose AAV therapy are 11.4, 10.1, 8.3 and 8.3 months. Although the two oldest cats have pronounced hind limb weakness, they are still able to walk, eat and use the litter box independently. Other than gait abnormalities due to hind limb weakness, they behave as relatively normal cats, playing with toys and siblings.The 8.3 month-old cats have very mild hind limb weakness and appear to be less affected neurologically than their older counterparts at the same age. The remaining younger cats treated with high-dose therapy are also doing well, and we have not observed any evidence of vector toxicity in cats to date. In a second arm of the study, 6 GM2 cats were treated with a low dose of AAV gene therapy, in preparation for dose escalation groups in the human clinical trial. Low-dose cats currently range in age from 5.7 to 6.8 months, all having lived longer than untreated GM2 cats (4.5 months). While all low-dose cats still walk easily and independently, they have hind limb weakness coupled with subtle but definite intention tremors, a typical sign of disease progression in untreated GM2 cats that is not apparent in the high-dose treatment group. Therefore, we are making progress toward defining the actual target dose for the human clinical trial.

In the sheep model of Tay-Sachs Disease, two of four affected sheep were treated with AAV gene therapy. Two of the affected sheep were left as untreated controls because this is a very new animal model whose disease progression is not yet well-characterized clinically. One of the untreated control sheep was euthanized before it reached a severe stage of disease so that tissues from a disease midpoint could be analyzed. The second untreated control sheep reached the endpoint of disease progression at 8.0 months of age and deteriorated very rapidly over the final 2 weeks of life. Both AAV-treated sheep currently are ~9.8 months old and walk independently but with subtle yet definite fore limb abnormalities. The treated sheep eat well and interact with humans and other sheep normally. While these results are encouraging, it is essential to remember that clinical disease progression in the sheep TSD model has not yet been thoroughly characterized and that we have no real idea of its natural variability from animal to animal. In fact, the untreated control animal that reached the endpoint at 8.0 months of age was, from the outset of the study, the most severely affected animal of the group. Therefore, it will require several more months of observation and analysis before any conclusions can be drawn regarding gene therapy success in TSD sheep.