Cure Tay-Sachs Foundation
Saving Lives
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Research Update – December 2010

The Tay-Sachs Gene Therapy Consortium (TSGT) has issued a research progress reports for public release and it contains information about cat research, sheep research and for the first time timeline and budget issues as they related to human clinical trials. We have come a long way since starting this journey. The Cure Tay-Sachs Foundation has spent $408,358 in support of the TSGT and the NIH awarded them a four year, $3.5 million grant in August 2009. The TSGT report is immediately following and we concludes this report with discussion about the funding hurdles the plan still faces.

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 overtime 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 planned 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

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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.

So what does this all mean? The research team continues to make outstanding progress in animal models and is pushing towards clinical trials now. To move to clinical trials there are funding and research challenges that still must be conquered. We need to manufacture GMP-grade vectors for testing and the clinical trials. The original plan called for corporate funding – but in this economic climate all the potential funders have declined. The vectors will cost about $870,000. The TSGT is pursuing other governmental funding sources but we might need to pay this with private sector funding. Additionally the TSGT needs to do toxicity studies. The toxicity studies are included in the NIH grant for September 2012. If we wished to accelerate the timeline (and we always wish to accelerate) – we'd need to find a funding source for this $445,000 study.

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The clinical trial requires a clinical severity scoring system for Juvenile TSD and SD patients. The first Natural History study provided insight into the disease progression in the Infantile disease, but finding enough Infantile patients for clinical trials would be difficult as the disease is so aggressive and often not diagnosed right away. The Juvenile population would be a preferred model for early clinical trials. The team is requesting $200,000 for expanded Natural History studies in Juvenile patients – including collection of medical records. And finally the TSGT will need experienced consulting assistance to navigate the complicated governmental regulations required to get the FDA to approve a clinical trial for a rare disease like ours; estimated cost $80,000. Once we get an approved clinical trial – the cost could be $2 million for the Phase I and Phase II components (likely to take place over a two year timetable).

The question is often asked – if we had unlimited funding could we accelerate this research? Today I think the answer would be yes. If we had the $1.6 million to cover the vector manufacturing, toxicity and natural history studies and consultants plus the $2 million need to fund the clinical trial – we could accelerate the plan 12 to 18 months. Today the clinical trials would begin in September 2013, the team would like to push for December 2012 and an aggressive plan exists that targeted March 2012 – but they are all contingent on achieving huge funding goals. The conventional wisdom is an approved FDA clinical trial has a good chance of receiving NIH grant support – it would mean another cycle of submission, review, and award – that could take 9 to 12 months. A larger pool of private support is also likely because we'd be fundraising for an FDA approved trial – not waiting on the NIH means faster. Today, we needed to focus on getting FDA approval as efficiently as possible – that makes our immediate challenge $1.6 million. The CTSF has $850,000 in uncommitted funds – and we are not in this alone.

This update will be posted on the Cure Tay-Sachs website under Quarterly Updates. You can also learn more about the TSGT at www.tsgtconsortium.com. If you have any questions or comments about this update I can be reached at ken.bihn@curetay-sachs.org or you can call the foundation offices at (216) 812-5855

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