

SHEEP AS A MODEL OF TAY-SACHS DISEASE

LAY SUMMARY

NATIONAL TAY-SACHS AND ALLIED DISEASES ASSOCIATION

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Four lambs with Tay-Sachs Disease (TSD) arrived at Auburn University early on the morning of April 17, 2010 at approximately 2 months of age. Two TSD lambs were showing disease signs upon arrival, and 1 lamb began to show clinical signs shortly after arrival. The first disease symptom in the lambs was “knuckling” of the front legs, a gait disturbance that causes affected lambs to stumble. In fact, gait problems later in life were the most reliable and consistent indicator of disease progression, and the study end point was reached when TSD lambs were unable to stand for 2 days.

Two of the TSD lambs (“Texas” and “Driver”) were treated with adeno-associated virus (AAV) gene therapy by injection directly into the brain (thalamus) and cerebrospinal fluid (CSF), which bathes the brain and spinal cord. Treatment was performed at ~3.5 months of age, or 6 weeks after the onset of clinical disease. Since the life span and disease course of untreated TSD lambs were unknown, 2 TSD sheep (“Glidden” and “Aiden”) remained untreated for comparison to treated animals.

While the life span of untreated TSD lambs was 8 months or less, AAV-treated sheep lived to 14.0 and 14.8 months of age, or almost twice as long as their untreated counterparts. In an attempt to learn the best therapy for future human clinical trials, Texas was treated with a combination of both Hex subunits (alpha and beta), while Driver was treated with the alpha subunit alone. Though both sheep survived to similar ages, treatment with both subunits produced dramatically higher levels of Hex activity in the brain (on average, almost 70 times higher Hex levels than treatment with the alpha subunit alone).

Other substantial progress was made in year 1 of the project, as summarized below:

- A. A baseline of disease symptoms (in addition to “knuckling”) was established, which will be important for evaluating therapeutic success in future tests.
- B. TSD sheep were safely and successfully treated with large-volume injections of AAV vector into the brain and CSF.
- C. Though TSD animals were treated ~ 6 weeks after symptom onset, AAV gene therapy was clearly beneficial. Also, later symptoms such as ataxia (clumsy gait) were delayed.
- D. MRI at 6 months of age demonstrated marked preservation of brain structures in AAV-treated versus untreated TSD sheep. However, the large horns of Jacob sheep prevented later MRI analysis. Currently, Jacob sheep are being outbred with a hornless breed to avoid this problem in future. Also, a stronger and larger MRI unit recently installed at Auburn University is being tested for sheep use.
- E. The cerebellum had normal or above-normal levels of Hex, even though it was treated indirectly through the CSF.
- F. Hex activity in the spinal cord of AAV-treated sheep was lower than expected (based on studies in other species), and further tests will be performed to better understand this finding. It will be important to learn whether higher Hex activity in the spinal cord leads to longer survival of TSD sheep.
- G. All TSD sheep (treated or untreated) were able to see at the study end point.
- H. Though they had obvious gait disturbances, TSD sheep (treated or untreated) lived relatively normal lives until ~10 days prior to end point, at which time they deteriorated rapidly.

Year 2 of the TSD sheep project began in late June, 2011, with a total of 12 affected sheep. While 2 animals were untreated, the remaining TSD sheep were divided into short-term and long-term treatment groups, with short-term studies aimed at further defining whether optimal treatment requires both Hex subunits. Tissues collected in December, 2011, are currently undergoing analysis, which will require several months. TSD sheep in the long-term study group (4 animals total) were treated after disease onset at approximately the same age as “Texas” and “Driver.” As stated above, even untreated TSD sheep are quite healthy until late in the disease course, after which they decline rapidly. Nevertheless, all AAV-treated sheep in the long-term group remain healthy and have minimal disease signs. They eat well, behave as normal sheep, and are quite difficult to catch in an open field.