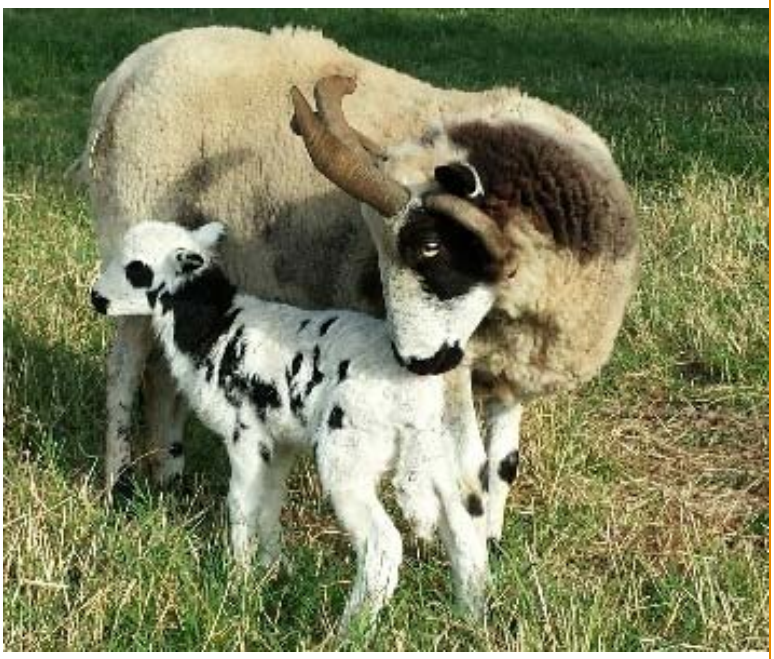
Three Year Study on Jacob Sheep Completed

Dr. Douglas Martin and his team of researchers at Auburn University have recently completed a three year study on sheep with Tay-Sachs disease (TSD). In addition to further characterizing this disease model, Martin's group conducted safety and efficacy studies of AAV gene therapy in the TSD sheep. Since the sheep have a mutation in the HEXA gene (and subsequent deficiency of Hexosaminidase A (HexA) protein), this is an authentic model of Tay-Sachs disease. Furthermore, the large brain size of the sheep allows researchers to confront certain challenges of gene therapy, including brain targeting and distribution.



The Details

- TSD sheep were treated by direct brain injection of AAV vectors encoding Hex.
- There were three different AAV vector designs and two different doses tested in the TSD sheep.

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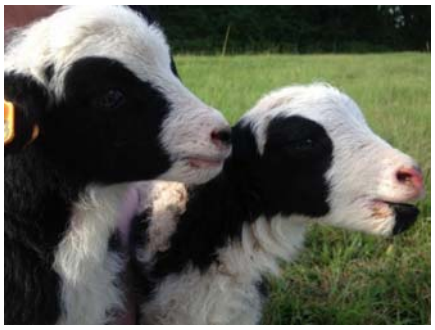


After years of loving care at St. Jude's Farm, thanks to Joan and Fred Horak, the flock was moved to the green pastures of Auburn University last year to continue their important contribution to Tay-Sachs Gene Therapy research. At least $27,000 needs to be raised for the next 6-9 months to continue the daily maintenance of the sheep. We need your help.

In addition to gifts, there are new lambs you can adopt and name for a minimum gift of $1,000. Contact Joan Lawrence at joan@ntsad.org for more information.

NTSAD and the Sheep

- TSD sheep were treated after the onset of symptoms in the mild to moderate disease stage.
- Both short and long-term AAV gene therapy studies were conducted.

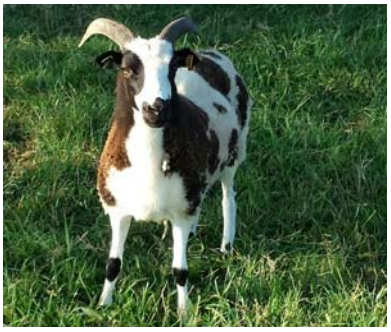
The Results

Survival

- Untreated TSD sheep had a disease onset of less than two months of age and lived an average of 9.1 months.
- When all AAV treated TSD sheep were combined (all vector designs and doses), average lifespan was 13 months of age, a 43% increase.
- The most successful AAV treatment group had a mean lifespan of 14.3 months, a 57% increase.

Enzyme activity/storage reduction

- As expected, levels of therapeutic enzyme were highest at the injection site and decreased with distance from the injection.
- With both dosages of the most promising vector design, all areas of the brain near the injection site had levels of enzyme above normal. In the more distal cerebellum (part of the brain that controls movement), enzyme levels were near normal with higher dose but substantially lower with the lower dose.
- Only the cervical region (closest to the brain) of the spinal cord showed Hex levels above background, and only the higher dose vector reached normal levels in this region. Complementary studies in Sandhoff disease cats produced much better distribution of enzyme to the spinal cord, which could be one factor in improved survival seen in cats.
- Ganglioside storage product was reduced in all areas of the brain near the injection site, but not significantly reduced in distant brain regions (i.e. cerebellum) or spinal cord. This was not surprising since the therapeutic Hex enzyme did not sufficiently reach these areas.
- Enzyme activity was low in all tissues analyzed outside the central nervous system (liver, heart, spleen, small intestine, and kidney). This is also different from AAV treated Sandhoff cats, in which enzyme activity can reach >50% of normal activity in some tissues and may account for



Read more **here** about this unique flock of sheep that NTSAD has supported over the years. In total, NTSAD has provided four grants amounting to over $300,000 to nurture the flock that has made enormous contributions to the gene therapy research.

A Special Note

NTSAD's Family Services Director, Kim Kubilus, has stepped down from her position as of August 1st. She decided after 12+ years at NTSAD to focus her energies on her two young children. She will thankfully remain a part of the NTSAD family serving on the annual conference committee and working with siblings, as she is one herself after losing two brothers to a rare genetic disease. She leaves big shoes to fill but we remain committed to continuing the great work she conducted over the years. Our many thanks to Kim for everything and best wishes to a healthy and bright future.

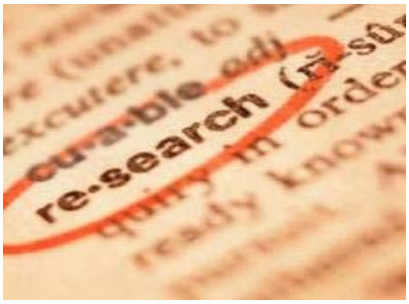
longer survival in the cats.

MRI and brain pathology

- MRIs were conducted on normal, untreated TSD sheep, and AAV treated sheep with a very high magnetic field (7 Telsa), allowing for superior quality brain images.
- MRIs showed that many changes caused by disease, including loss of myelin, were improved after AAV gene therapy.
- Untreated TSD sheep brains showed pronounced neuroinflammation upon histological examination (inflammation of brain tissue seen when looking at the brain with a microscope). AAV gene therapy was found to decrease but not fully prevent this response.

Going Forward

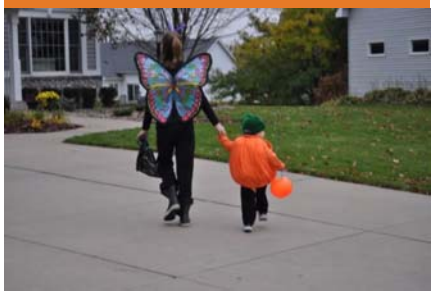
- One gene therapy treated sheep is still alive and doing well at almost 1.5 years of age and continues to be monitored regularly.
- The flock was moved from Texas to Auburn University in May of 2013, which will allow the project to grow.
- The veterinarians at Auburn University had a very successful first breeding season with 13 lambs already born and two more expected in the near future. (Contact Joan Lawrence at joan@ntsad.org to adopt and name one of the lambs to support this important program.)
- Dr. Martin and his team of researchers will continue to optimize gene therapy in the sheep model of TSD, primarily focusing on better distribution of the enzyme to more distal brain regions (cerebellum) and the spinal cord.



Research + Funding = Hope

Support Research with a gift here.

Read more about current and past grants funded by NTSAD on our website here.



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A lone sheep cries out. There are more of us than them. The flock keeps grazing.
A Sheep Haiku from Achill Island, Ireland

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