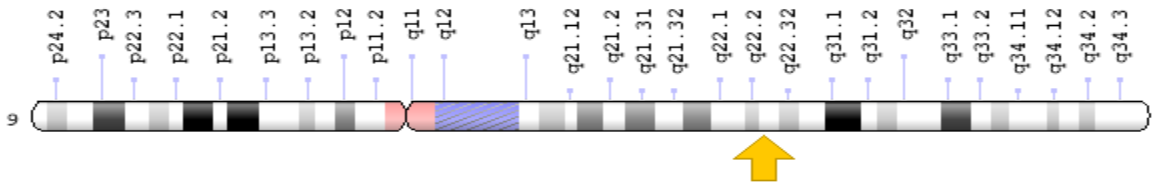
Deater Foundation, Inc.

PO Box 255
White Deer, PA 17887

The purpose of the Deater Foundation is to provide funding for medical research on the disease Hereditary Sensory and Autonomic Neuropathy Type1 to discover a treatment or cure.

Hereditary Sensory and Autonomic Neuropathy Type1 (HSAN1) is an autosomal dominant disease caused by an error in the genetic code (the DNA). Autosomal DNA describes DNA which is inherited from any of the numbered chromosomes. Humans have 22 pairs of autosomes and one pair of sex chromosomes. In an autosomal dominant disease, only one of the parents must have the deviant chromosome for the disease to be passed on to the offspring. The child could inherit the "good" chromosome from the affected parent and the "good" chromosome from the unaffected parent and be well, or could inherit the deviant, or "bad" chromosome from the affected parent and the "good" chromosome from the unaffected parent. Each child has a 50/50 chance of inheriting the deviant chromosome.



Researchers have found at least four genes responsible for hereditary sensory neuropathy type 1 (HSAN1). The research that is currently being supported by the Deater Foundation is centered on the mutation in the SPTLC1 gene. The SPTLC1 gene provides instructions for making one part (subunit) of an enzyme, serine palmitoyltransferase (SPT). The SPT enzyme is involved in making certain fats called sphingolipids. Sphingolipids are important components of cell membranes that play a role in many cell functions.

Deater Foundation Inc. Treasurer's Report

Balance as of 6/01/16	**$44,453.11**		
Income:		**Expense:**	
Contributions 6/1/16 to 12/31/16	7,134.74	July 2016 U Mass Donation	-20,000.00
Interest 6/1/16 to 12/31/16	6.45	Symposium Deposit Royal Sonesta Hotel	-7,576.12
Contributions 1/1/17 to 5/31/17	9,799.39	PayPal Service Charges	-5.74

Interest 1/1/17 to 5/31/17	1.22	
Balance as of 5/31/17	**$33,813.05**	

Research Funded by the Deater Foundation

We are very pleased to provide this update on progress toward devising methods to silence the SPTLC1 gene as a potential therapy for HSAN1. We have made progress in three areas. The key point is that we have now developed two types of reagents that can silence the SPTLC1 gene.

One type of reagent is composed of small strings of ~ 20 molecules of nucleic acids (antisense oligonucleotides or ASO's) that have sequences complementary to specific sequences in the SPTLC1 gene. The concept is that these ASO's bind RNA from the target gene and thereby activate enzymes that break-up the RNA, preventing it from making protein. As we have reported before, we have been fortunate to have Havisha Karnam as a graduate student working in conjunction with Anastasia Khvorova Ph.D. on this project. Dr. Khvorova is an internationally recognized expert in the chemistry of ASO's. With Dr. Khvorova's guidance, Havisha has used two types of chemistry (designated LNA gapmers and hsiRNA) to generate ASO's that can silence SPTLC1. In particular, she has developed ASO's that specifically target hamster SPTLC1 and not mouse, and reciprocally. She also now has ASO's that target human SPTLC1. We need ASO's that target hamster and not mouse because as you recall our mouse model of HSAN1 has the HSAN1 mutations in a hamster transgene added to each cell above and beyond the normal mouse SPTLC1 gene. In our last report, Havisha had made good progress in developing these reagents. However, over the last four months she has obtained optimized reagents and, most recently, has shown she can use them to shut off the hamster SPTLC1 gene (but as desired not the mouse gene) in neuronal cultures derived from the transgenic HSAN1 mice. As a positive control, Havisha has also shown that she can silence other genes in the spinal cords of normal mice (such as the normal huntingtin gene). We are very excited with this development because this is an important step toward testing anti-SPTLC1 ASO'S directly in the HSAN1 mice. These ASO's are intended to be given into the spinal fluid. In patients, this would likely require multiple doses each year via LP.

The second type of reagent we have developed are microRNAs (miRs), the elements we described to you in our proposal last fall. These are very much like ASO's except that these small strings of nucleic acids are made up of RNA (while the ASO's above are made of hybrids of RNA and DNA, with chemical modifications). The miRs have been developed in conjunction with Dr. Chris Mueller, Dr. Li Yi and another graduate student, Gabrielle Toro. For this project, they have developed some new assays (using a technique called digital PCR) to be able to quantify with precision the levels individually of mouse, hamster and human SPTLC1 RNAs. In parallel they have also generated two miRs that target human SPTLC1 and one that targets hamster SPTLC1. They have also taken two of the reagents developed by Havisha (above) to target the hamster SPTLC1 and converted them from LNA gapmer and hsiRNA chemistries to make miRs. These new miRs against hamster and human have been

devised in a form that let's us put them into a virus commonly used by Chris Mueller, known as adeno-associated virus (AAV). (In fact, the head of the Gene Therapy Center at UMass patented scores of these AAVs). We and others have found that with two newer types of AAV (labeled AAV9 and AAVrh10) one can get excellent penetration of AAV into the spinal cord and brain, and thereby have the cargo carried by AAV released into the interior of brain and spinal.

Our goal in the next 2-3 months is to complete the process of packaging our new anti-SPTLC1 miRs into the AAV and to use this system to treat our HSAN1 mice. In the long term, one hopes that this will be a useful clinical strategy in people. A particular advantage of AAV is that when it delivers new genes or miRs to the brain and spinal cord tissues, it permits extremely long-term (many years) expression of the cargo gene or miR. This means that, by contrast with the ASO therapy above, this AAV-mediated delivery of the anti-SPTLC1 miR could potentially result in years of treatment from a single injection. Some describe this as "one and done". A downside of this approach is that there is no way to retrieve the virus or turn off its cargo once it is delivered. These points not withstanding, our view is that this is a powerful therapeutic approach that warrants testing in any human disease in which a mutant gene is somehow adverse or toxic.

On a third front, a post-doc in my lab is also working on aspects of HSAN1 as one of two projects. Her goal is to get the assay for the deoxysphingoid bases (DSB) up and running here at UMass. We have been greatly assisted in this endeavor by Thorsten Hornemann who has provided protocols and details. Importantly, our plan is to test some samples that he also tests, so that we can be assured that we are measuring DSB levels identically to his lab. Hirosha is a careful scientist who is well on the way to getting this method running. This will help us enormously as we do more testing of our silencing therapies in the HSAN1 mice.

On a parallel note, I want to mention that we have been extremely fortunate to have a very capable technician running our HSAN1 mouse colony. It is robust in numbers, suggesting that we should be in an excellent position to test the above reagents. I anticipate that the mouse-based testing will begin in the next 2-3 months.

On behalf of everyone here working on HSAN1, I want to offer my most sincere and heartfelt thanks for your support for our work. It has been quite consequential as we pursue the above two approaches to silencing the SPTLC1 gene. Also, we want to thank you for once again sponsoring the HSAN1 conference in Cambridge this spring. As before, it was scientifically illuminating and ultimately very motivating.

I look forward to remaining in close touch on all of these issues.

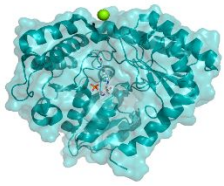
Sincerely,

Robert H. Brown, MD, DPhil

HSAN1 CONFERENCE April 18-21, 2017

An international cadre of experts gathered in April in Boston to discuss the chemistry, biology, genetics, neuropathy, treatment, and potential for cure for HSAN1.They were joined by post-doctoral fellows, doctors, researchers, and 5 members of the Deater family. The welcome dinner provided time to fellowship and talk about funding issues and possibilities, as well as to remember Larry Deater and his dedication to this ongoing research.

Dominic Campopiano- Edenborough Scotland- discussed the basic chemistry of the biosynthesis of the enzyme serine palmitoyltransferase (SPT). The SPTLC1 gene provides instructions for making one part (subunit) of the SPT enzyme. The mutation of the gene interferes with the mechanism of the enzyme SPT. A question that remains is, “how is SPT regulated by the cell?”



Teresa Dunn-Giroux- Bethesda Maryland- is focused on identifying and characterizing the enzymes responsible for sphingolipid synthesis, on determining how sphingolipid synthesis is regulated, and on clarifying the functions of these important lipids through a genetic and biochemical approach. The enzyme is more complex than previously thought.

Thorsten Hornemann- Zurich Switzerland- discussed the role of sphingolipids in the body. They play a major role in the neurological system- brain and nerves. We know that the blood levels of deoxysphingolipids is increased in HSAN1 because of the increased activity of the cells with alanine vs. serine. A similar increase is seen in persons with diabetes.

Garth Nicholson- Sydney Australia- talked about the difficulty of measuring the sensory progression in HSAN1 neuropathy because the nerve fibers at the point at which the affected person can feel are already depleted.

Naomi Chuying- presented her research on L-serine therapy in mouse models of diabetic neuropathy. She observed that deoxysphingolipid levels were elevated in Type II but not Type I Diabetes. L-serine supplementation improved gut transit time and pain response in mice.

Reza Seyedsedjadi- Massachusetts General Hospital- talked about questions that are asked to elicit responses that are used to measure symptoms. Some items are more sensitive than others and it is important in determining the natural history of the disease to have valid comparisons based on clear questions.

Hirosha Geeklyange- University of Massachusetts- discussed the role of sphingolipids in Alzheimer's Disease. Ceramide, a sphingolipid, is found at 3 times the normal levels after death in patient with Alzheimer's disease.

Vera Fridman- Denver Colorado- reviewed the results of the L-serine supplementation study. Half of the participants received L-serine and half received a placebo for a year. The second year all participants received L-serine. Standard nerve conduction tests were not sufficient to measure the study results. Patient reports were the most important and responsive results, along with positive reductions in the Chacrot-Marie-Tooth neuropathy scale.

Bob Brown and Havisha Karnam- University of Massachusetts- underscored that the mutant gene leads to neurotoxicity and targeting the gene may be the most reliable route to a cure of the disease by either suppressing or silencing the mutant gene. Working with Dr. Anastasia Khvorova, Havisha has determined that correcting the mutant gene in the neuron (dorsal root ganglia) may not be sufficient and treating the liver must be considered.

Anne Louise Oaklander- Massachusetts General Hospital- discussed her work on small fiber neuropathy and presented case studies of children. She is interested in studying children with neuropathy and suggests that microneuropathy, an electrophysiological technique used for recording nerve traffic directly from peripheral nerves may be helpful in imaging HSAN1.

Florian Eichler- Massachusetts General Hospital- talked about targeted gene correction to the dorsal root ganglia. In the L-serine study, the signal in motor and sensory nerves were modified by L-serine. He suggested engaging with industry to promote amino acid supplementation, but noted there is a critical limit of serine. Many questions remain. Is there a modifier gene? What is the actual cause, along the biologic pathway? The disease is present before any symptoms are manifest. A study in younger people, especially children, may be helpful.

The discussion and sharing of research ideas was invaluable, as participants asked questions of one another and discussed collaborations. The conference concluded with renewed dedication to seeking a long-term treatment and eventual cure for HSAN1.

This HSAN1 conference was fully funded by the Deater Foundation, Inc.

enterprise Foundation Donation

Once again, we give thanks for Deater Foundation Board member **Jon Ellsworth** and his employer **Enterprise Rent-A-Car**. The Enterprise Holdings Foundation awarded the Deater Foundation, Inc. a grant of $5,000.00. This is the 11th year Enterprise has donated to support the Deater Foundation!
"The Enterprise Holdings Foundation gives back and strengthens through charitable support the thousands of communities where our employees and their customers work and live."
Have you checked with your Human Resources Department to see if your employer is associated with a Foundation that might do the same?

L-Serine Study Results

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DELAYED-START TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF L-SERINE IN SUBJECTS WITH HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE 1 (HSAN1)

Vera Fridman1, Peter Novak2, William David3, Anne Louise Oaklander3, Eric Macklin3, Diane McKenna-Yasek2, Kailey Walsh3, Robert Brown2, Thorsten Hornemann4, Florian Eichler3 1University of Colorado Medical Center, Denver, US., 2University of Massachusetts Medical School, Worcester, US.,3 Massachusetts General Hospital (MGH), Boston, US., 4University Hospital Zurich, Clinical Chemistry, Zurich, Switzerland.

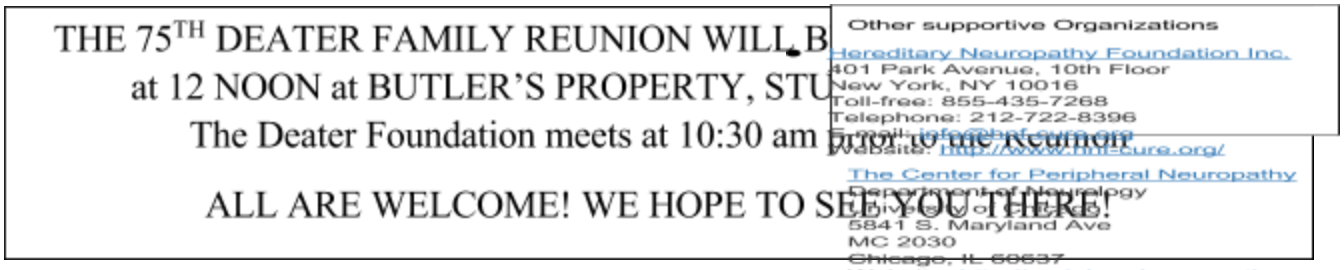
Introduction: Hereditary Sensory Autonomic Neuropathy Type 1 (HSAN1) is a severe, autosomal dominant, axonal neuropathy that manifests with marked, small fiber predominant sensory loss, variable degrees of limb weakness, and skin ulceration. HSAN1 is caused by mutations in the SPTLC1 and SPTLC2 genes, which encode two of the three subunits of the enzyme serine palmitoyltransferase (SPT). Mutations in SPT induce a permanent shift in the substrate preference from serine to alanine thereby forming a class of neurotoxic deoxysphingolipids (dSL). Supplementation with L-serine reduces dSL levels in transgenic HSAN1 mice and results in clinical improvement of neuropathy. We report a

two-year, delayed-start, placebo-controlled clinical trial evaluating the safety and efficacy of oral L-serine (400 mg/kg/d) in human subjects with HSAN1.

Results: All but 2 subjects (both of whom were in the placebo group) completed the study. At 1 year, participants randomized to L-serine experienced a significant decline in CMTNSv2 (Charcot-Marie-Tooth Neuropathy Scale version 2) relative to placebo (-1.8 units, 95% CI -3.3 to -0.3, p = 0.02). Both groups experienced improvement in the second year of the study, and the difference in CMTNSv2 diminished. (-1.45 units, 95% CI -3.7 to 0.81, p=0.20). The three items that contributed most heavily to benefit from L-Serine supplementation at 48 weeks included sensory symptoms, arm strength and leg strength. dSL levels declined significantly among subjects on L-Serine vs. those on placebo after one year of treatment: 41% decrease in 1-deoxy-sphingosine vs. 9.2% increase on placebo (p=0.001); and 59% decrease in 1-deoxy-sphinganine vs. 11% increase on placebo, (p < 0.001). Skin biopsy in the majority of subjects showed no detectable nerve fibers in the distal calf. IENFD (intraepidermal nerve fiber density) findings in the thigh were highly variable and preliminary analysis did not show a significant difference between the two treatment groups. AFT (autonomic function testing) showed only minimal change over time with no significant difference between the two groups.

Conclusions: L-serine is a safe and potentially efficacious treatment option for patients with HSAN1. L-Serine supplementation suppresses dSL levels in subjects with HSAN1 to near normal levels. IENFD on skin biopsy does not reliably capture progression in HSAN1.

Excerpts from the Poster Presentation given at the American Neurological Association



Your Support is Vital

Research requires a lot of investment! Financial contributions to the Deater Foundation are dedicated to the research that directly impacts the Deater family and other families facing similar challenges with HSAN1. This last year, your donations funded progress in gene modification and a dynamic opportunity for researchers to share ideas. Progress is being made, and the Deater family and Deater Foundation are part of it! We must press on.

Think of your brothers and sisters, aunts and cousins who gave their time, blood, and biopsies in hope of a cure. Hold a garage sale, turn in your old cell phone at the reunion, check with local foundations and your employer for contributions, donate in someone's honor. Together, we can do this! Thank you.

From the President

In April, my wife Cindy and I had the privilege of attending the 4th international symposium on HSAN1 funded by the Deater Foundation Inc. in Boston, Mass. As in the past, this collaboration of the top researchers from around the world in neurology, biology, and chemistry, to name a few, proved to be exciting and uplifting. The fact that these doctors put their practices and lives on hold, left their families in Australia, Switzerland, Scotland, Colorado and others, to spend three days discussing the disease that has affected our family for generations is overwhelming to me. I am thankful for these people and for the Deater Foundation Inc. board of directors, who dedicate their efforts to the best possible use of Foundation resources. I would also like to thank everyone that made a monetary donation to DFI and point out that we are a totally volunteer organization and that nearly 100% of your donation goes directly to funding research. Of the monies spent in 2016/17, only the PayPal service charges didn't go to expanding research. This is a necessary fee associated with the convenience of accepting online donations but it accounted for only 0.0002% of the Foundations expenditures last year. In this age of "fat cat" volunteer organization directors, I am proud to be part of an organization that truly values your donation and the progress we have made toward finding a treatment and cure for HSAN1 because of it. The Deater Foundation Inc. annual business meeting is held in conjunction with the Deater Family reunion, July 22 this year, and is open to everyone so you are welcome to join us at 10:30am. On behalf of Cindy, Ellen, Gary, Jon, Kyle, Nancy, Tami, Tonja and myself, thank you again for your contributions and support.

Sincerely,

Eric Newcomer