



NTSAD Research Initiative Grant Recipient, Dr. D'Azzo Completes Two-Year Project

Research led by **Alessandra d'Azzo, PhD** has revealed commonalities between **sialidosis**, a rare pediatric lysosomal storage disease, and Alzheimer's disease (AD), a severe neurodegenerative condition that usually develops in older adults.

The connection lies in the lysosomal enzyme Neuraminidase 1 (Neu1), which brain cells normally use to digest glycoproteins. A deficiency of the Neu1 enzyme has been known to result in sialidosis; however, this latest research reveals that animals lacking the enzyme also develop plaques, or abnormal clumps of proteins, in the brain that are typically seen in AD.

Summary of the Results

Edited by Allison Bradbury, PhD and Staci Kallish, DO

- * Results collected in year one of this 2-year study were published in *Nature Communications* in November 2013. The full article can be found at [here](#).
- * Brain injection of an **adeno-associated viral (AAV)** vector encoding NEU1 was used to increase the activity of Neu1 (the enzyme responsible for **sialidosis**) in a mouse model of AD. Elevating Neu1 proved to decrease the number of plaques by approximately 44% and reduced damage associated with AD disease in these mice.
- * Genetic studies in the sialidosis mice found 17 genes that were dysregulated, 10 upregulated and 7 downregulated. 2 of these genes, ApoE and alpha 2 microglobulin, are also altered in AD disease and further connect these two diseases. Analysis of these 17 genes of interest is still ongoing.
- * Further genetic analysis from a specific brain region,

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Brett and Eileen Linzer established [QuinnMadeleine](#) (QMI) in 2014 to honor their daughter who passed away last year from Niemann-Pick Type A.

Niemann-Pick Type A and Tay-Sachs are both lysosomal storage disorders with systemic and neurological degeneration. Because of this similarity and the promise of gene therapy to help treat both of these diseases, QMI decided to partner with NTSAD on the Jacob Sheep Project.

QMI has already raised \$6,000 for NTSAD to send to Auburn University where the sheep reside, and they are continuing their effort to raise more money to maintain the sheep. *Our many thanks to*

the hippocampus, of sialidosis mice was used to evaluate changes in a number of pathways over time. Analysis at 1 and 5 months of age demonstrated a correlation between disease progression and alterations in pathways related to **lysosome**, inflammation, and immune responses.

* In addition to genetic analysis of the brain, evaluation of proteins in the **cerebrospinal fluid (CSF)** of sialidosis mice was also conducted. Levels of lysosome related proteins such as cathepsin D and cathepsin B were found to be altered in the CSF of sialidosis mice. Other proteins that have been previously been identified as potential **biomarkers** for AD were also altered in the CSF of the sialidosis mice (e.g. CATD and fibrinogen).

* Analysis of the level of activity of lysosomal enzymes was also conducted on the CSF of sialidosis mice and revealed increased activity of alpha-mannosidase and beta-hexosaminidase, an indication of lysosomal dysfunction. Close examination of the brain structure that secretes CSF, the choroid plexus, showed changes in the shape and signs of disease commonly associated with **lysosomal storage disorders**.

How Does This Research Help?

The study allowed a better understanding of lysosomal function, which may be useful in understanding all LSDs. These results demonstrate that Neu1 deficiency could also be a risk factor for AD later in life. Furthermore, these studies identified upregulation of specific genes and proteins in sialidosis mice that have previously been associated with AD. These results could provide common targets in which to develop therapeutic agents that could have implications in both sialidosis and AD.

Who is Alessandra D'Azzo, PhD?

Alessandra d'Azzo received a PhD in Genetics in 1973 from the University of Milano, Italy; and a PhD (cum laude) in Medical Cell Biology and Genetics in 1982 from the Erasmus University, Rotterdam, The Netherlands. In 1982 she joined the lab of Dr. Elizabeth Neufeld at the National Institutes of Health and worked on clinical variants of GM2-gangliosidosis and Tay-Sachs disease. After research work at Erasmus University in The Netherlands, Alessandra joined the Faculty of St. Jude Children's Research Hospital in 1993, and together with her husband, Dr. Gerard Grosveld, started the department of Genetics and participated in the development of the St. Jude Transgenic Core Facility.



Quinn's family for supporting our research efforts!



[Make a gift here](#) to support the Jacob Sheep and keep research progress moving in the right direction!

Our **Day of Hope** continues to be observed with events happening in Alabama, Florida and Pennsylvania in the coming weeks.

[The Lowery Family Yard Sale](#)

In honor of Jacob
October 16-18, 2014
Jemison, Alabama

[9th Annual Lacie's Legacy Memorial Walk](#)

In memory of Lacie
October 18, 2014

[The Mathew Forbes Romer Foundation's Hoops for Hope](#)

In honor of Mathew
October 25, 2014
Boca Raton, Florida

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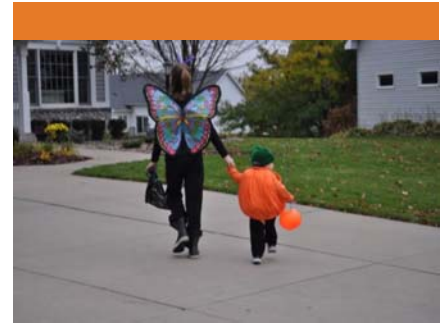
Dr. d'Azzo is currently a Full Member of the Genetics Department and an Adjunct Professor in the Department of Anatomy and Neurobiology at the University of Tennessee Health Sciences Center. She holds an Endowed Chair in Genetics and Gene Therapy.

Dr. d'Azzo has a longstanding interest in the processes that control lysosomal and proteasomal degradation, and is a leading scientist in the field of lysosomal storage diseases (LSD). Her research continues to focus on the two glycoproteinoses, sialidosis and galactosialidosis, and the glycosphingolipidosis, GM1-gangliosidosis. Her scientific accomplishments in this field include the discovery of the primary defect in galactosialidosis and the generation of mouse models for these three disorders. Her seminal studies of the molecular mechanisms of pathogenesis in these pediatric LSDs have uncovered new functions of lysosomal enzymes and their physiological substrates in basic cellular processes that influence the course of disease progression of common adult neurodegenerative diseases, like Alzheimer's disease.

Her findings may have important implications in the biology and treatment not only of LSDs but also of severe and incurable disease conditions affecting primarily the adult population.

Dr. D'Azzo wrote, "The longstanding interest of my laboratory has been in the study of lysosomal storage diseases affecting glycolipid and glycoprotein metabolism. Throughout my career I worked towards one goal: to bring discoveries made at the bench side to the bedside in order to improve the quality of life and ultimately treat children with these disorders."

our website [here](#).



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"A little progress every day adds up to BIG results." - Satya

national tay-sachs & allied diseases association

susan kahn, executive director (skahn@ntsad.org)
joan lawrence, director of development (joan@ntsad.org)
diana pangonis, communications manager (diana@ntsad.org)
ingrid miller, office manager (ingrid@ntsad.org)

2001 beacon street, suite 204
boston, ma 02135
(617) 277-4463
www.NTSAD.org

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