

Indications™

Newsletter of The Lysosomal Disease Network™

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Keys to Understanding the Lysosomal Disease Network

A Closer Look at Completed Lysosomal Disease Network Pilot Studies

By Evelyn S. Redtree, M.S.

The Lysosomal Disease Network (LDN) is in the fifth year of its first five-year NIH research contract (contract number U54NS065768). Research protocols that have been pursued during this funding cycle have included several pilot studies. Interested researchers may be wondering what can be accomplished during the limited study period and limited funding inherent in pilot studies. To elucidate this question, pilot studies will be examined in some detail.

“Characterizing the neurobehavioral phenotype(s) in MPS III” is LDN pilot study Protocol # 6707. This was an observational pilot study whose Principal Investigator was Michael Potegal, Ph.D., Associate Professor of Pediatrics, the University of Minnesota, Twin Cities campus. Sub-investigators included Elsa Shapiro, Ph.D., Chester Whitley, Ph.D., M.D. (genetics), Kath-

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Meet Our Patient Advocacy Groups

The LDN considers itself lucky to have dedicated patient advocacy groups as members of the Network. This issue, we present with gratitude . . .



National Tay-Sachs & Allied Diseases Association

<http://www.ntsad.org/>

The National Tay-Sachs & Allied Diseases Association (NTSAD), based in Boston, Massachusetts, was founded in 1957 in New York by a small group of concerned parents with children affected by Tay-Sachs disease, other sphingolipidoses, or related genetic disorders. There are currently no treatments for these diseases; they are fatal in children and progressively disabling in their adult onset forms. The mission of the National Tay-Sachs & Allied Diseases Association is to lead the effort to treat and cure Tay-Sachs and related genetic

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The **Lysosomal Disease Network** (U54NS065768) is a part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network (RDCRN), supported through collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.



Keys to Understanding the Lysosomal Disease Network

A Closer Look at Completed Lysosomal Disease Network Pilot Studies

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leen Delaney (neuropsychology), Brianna Yund (neuropsychology), Igor Nestrasil, M.D. (brain imaging), Alia Ahmed, M.D. (brain imaging), Robin Rumsey, Ph.D., (autism and neuropsychology). Additional funding was generously provided by Shire and the National MPS Society.

The primary objectives of this pilot study were to test these four hypotheses: (1) children with MPS III (Sanfilippo syndrome) will show more hyperlocomotion, fearlessness, asociality and noncompliance than children with MPS IH (Hurler syndrome) of similar cognitive ability; (2) these behaviors will become more frequent and/or intensify over time, consistent with the Cleary and Wraith (1994) model; (3) loss of cognitive and language function as measures of neurologic decline will directly precede or co-vary with behavioral decline; and (4) children with MPS III will show more autism-related symptoms over time and will meet criteria for Autism Spectrum Disorder.

The overarching goals were to identify the behavioral phenotype, and its neural basis, in MPS III; and to answer the questions: is the behavioral phenotype similar to that of Klüver–Bucy syndrome and to Autism Spectrum Disorder? Is there evidence for amygdala abnormality in relation to these two sets of behavioral abnormalities?

A secondary objective was to develop a sensitive and specific behavioral rating of disease progression in MPS III that can be used for clinical outcome studies.

Planned enrollment for this pilot study was 40 MPS III type A or B patients, and 10 controls (children matched for age who are post-hematopoietic stem cell transplantation (HCT) for MPS IH, and who have low cognitive function). The 40 MPS III type A or B participants needed to have a verified diagnosis of MPS IIIA or MPS IIIB (proof of genetic mutation, or

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Dr. Pamela M. McInnes Appointed as NCATS Deputy Director and Acting Director of Office of Rare Diseases Research

Pamela M. McInnes, D.D.S., has been named Deputy Director of the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health. Upon the February 8, 2014 retirement of Stephen C. Groft, Pharm.D., long-time Director of NCATS' Office of Rare Diseases Research (ORDR), Dr. McInnes was also appointed as Acting Director of ORDR during the search for a new director.

The author of more than 40 peer-reviewed articles and five books, Dr. McInnes first joined NIH in 1989 as a grants associate for its Office of Extramural Programs in the Office of the Director. Before coming to NIH, she served in academic and consulting roles at the Louisiana State University Medical Center, Shreveport. Dr. McInnes earned her D.D.S. and M.S. degrees from the University of the Witwatersrand, in Johannesburg, South Africa, where she also lectured prior to coming to the United States.

NCATS Director Christopher P. Austin, M.D. said, "I am thrilled that Pamela is joining the NCATS leadership team. Her expertise in translational and clinical research coupled with her extensive extramural management experience, and her record of accomplishment in trans-NIH and public-private collaborations, make her an ideal fit as our deputy direct-



Pamela M. McInnes, D.D.S.

or. Her recruitment is a key milestone in our building the NCATS organization into a catalyst for transformational change in translational science, getting new treatments to more patients more quickly."

Prior to her appointment as Deputy Director of NCATS, Dr. McInnes served as Director of the Division of Extramural Research at the National Institute of Dental and Craniofacial Research (NIDCR). At NIDCR Dr. McInnes

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A Closer Look at Completed LDN Pilot Studies

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enzymatic analysis prior to enrollment in study). They also needed to be older than 2 years and be able to walk.

The MPS IH post-HCT control participants needed to be between 2 and 5 years of age, and to be able to walk without support. This study's exclusion criteria were simply if participants were unable to cooperate or comply with study procedures, or participants who, in the opinion of the investigators, were disqualified by other limiting co-existing conditions, such as severe hearing or visual impairment.

The pilot study succeeded in enrolling 30 children with MPS IIIA and 10 children with MPS IIIB, and 8 post-HCT MPS IH patients. Study procedures involved placing each subject, (one subject at a time), in an experimental "risk room." The room contained attractive and mildly frightening objects, exposure to a 92 dB startle noise triggered by contact with an attractive toy, mother's return after a brief absence, and compliance with her cleanup directive. The investigators' results showed that children with MPS IIIA: (a) left mother sooner, (b) wandered more, (c) were more likely to approach frightening objects, (d) were less likely to respond to loud noise with whole-body startle, (e) were less likely to avoid the toy associated with the startle noise, (f) interacted less with mother upon her return, and (g) complied less with her cleanup command. These findings, together with parental ratings, confirmed a Klüver–Bucy-like syndrome.

Klüver–Bucy syndrome is associated with loss of amygdala function. Brain magnetic resonance imaging (MRI) of the children with MPS IIIA showed volume loss that was greater in the amygdala than in the hippocampus and cortical gray matter; only amygdala loss correlated with reduced fearfulness. MPS IIIA may be the first identified pediatric disease presenting systematically as a Klüver–Bucy syndrome variant. If validated by further studies, the



Klüver–Bucy syndrome hypothesis of MPS IIIA would provide important clinical and theoretical information for the guidance of families, as well as markers for natural disease progression and treatment effects.

In addition, every participant also was administered the Autism Diagnostic Observation Schedule, the standard method for identifying autism spectrum disorders in the general population, to understand the behavioral evolution of these symptoms in MPS III. It was found that in MPS IIIA all children older than 46 months of age met the criteria for ASD, compared with only two of ten children aged less than 46 months. Social and affective (emotional) abnormalities were the cause of this; restricted interests and repetitive behaviors were mostly absent. Although ASD symptoms were more frequent in the severely cognitively impaired children, such behaviors were observed across the entire range of cognitive impairment.

Work continues for MPS IIIB and on the analysis of the Sanfilippo Behavior Rating Scale.

Publications resulting from LDN protocol number 6707:

M. Potegal, B. Yund, K. Rudser, A. Ahmed, K. Delaney, I. Nestrasil, C.B. Whitley, E.G. Shapiro, Mucopolysaccharidosis Type IIIA presents as a variant of Klüver–Bucy syndrome. *J Clin Exp Neuropsychol* 35(6) (2013) 608-616. PMID: PMC3931576.

R.K. Rumsey, K. Rudser, K. Delaney, M. Potegal, C.B. Whitley, E.G. Shapiro, Acquired Autistic Behaviors in Children with Mucopolysaccharidosis Type IIIA. *J Pediatr* 164(5) (2014) 1147-1151.e1. PMID: PMC4041612. [Available on 5/1/2015]

Don't Forget . . .



Peer-review manuscript submission deadline for Elsevier's *Molecular Genetics & Metabolism* special February 2015 "Lysosomes" issue is **September 1, 2014**. Be sure to clearly state that you intend your submission to appear in that "Lysosomes" issue. Visit: <http://ees.elsevier.com/mgm/>

LDN Research Matters



Protocol #6713: A Natural History Study of Gangliosidosis and Other Hexosaminidase Deficiencies

Lysosomal Disease Network longitudinal study number 6713, led by Chester B. Whitley, PhD, MD, seeks to ascertain the natural history of the gangliosidoses, which are the hexosaminidase deficiency diseases Tay–Sachs, Sandhoff, and late-onset Tay–Sachs (LOTS), and GM1 gangliosidosis. To learn more about the gangliosidoses, read the “Check Your Knowledge” article on page 11. Dr. Whitley is the Principal Investigator of the Lysosomal Disease Network and is a metabolic disease physician and researcher at the University of Minnesota Twin Cities campus. The co-investigator of this LDN protocol is Florian S. Eichler, MD, Assistant Professor of Neurology, Harvard Medical School; and Assistant in Neurology, Massachusetts General Hospital, and Director of its Leukodystrophy Clinic.

This longitudinal study represents the first attempt to collect and quantify the natural history of the gangliosidoses. The anticipated sample size is 15 Tay–Sachs/Sandhoff disease and 15 LOTS disease patients. The number of enrolled subjects will be large enough to detect trends and differences. Neuropsychological data can be compared to the norms for children of a certain age. In addition to clarifying the natural history of the gangliosidoses, this longitudinal study seeks to (1) better understand the heterogeneity of these diseases; (2) to use the data collected on disease progression to develop an objective disease stage and severity index; (3) to use the data collected on disease progression to determine the

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Dr. Pamela M. McInnes Appointed as NCATS Deputy Director and Acting Director of Office of Rare Diseases Research

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was responsible for all of the Institute’s extramural research, ranging from basic through clinical research, including large and complex clinical and population-based trials. She demonstrated solid commitment to rigorous and robust conduct of clinical trials adhering to the highest standards for human subject protection and data integrity. Her work in translational sciences resulted in numerous product development and clinical evaluation programs. Dr. McInnes has been actively engaged with the broader extramural research community in efforts to reduce morbidity and mortality attributable to a large spectrum of diseases and disorders.

Prior to her time at NIDCR, Dr. McInnes spent 16 years at the NIH’s National Institute of Allergy and Infectious Diseases (NIAID), where she served in many capacities, including Deputy Director for its Division of Microbiology and Infectious Diseases. In this role she oversaw extramural research branch programs in infectious diseases and microbiology. Concurrently she served as Associate Director for Clinical Research, and had responsibility for the reorganization and oversight of the complex and diverse Divisional Clinical Research Program. Her work on contract awards to develop recombinant RPA anthrax vaccines and attenuated smallpox vaccines required extensive collaboration and interactions with the Food and Drug Administration, Department of Defense, and Centers for Disease Control and Prevention. Another of her many accomplishments at NIAID was oversight of the scientific design and programmatic implementation of its Challenge Grant Program. The goal of this initiative was to promote joint ventures between NIH and biotechnology, pharmaceutical and medical device industries to reduce significantly the impact of infectious diseases nationally and worldwide.

Source information for this article was provided by the National Institutes of Health, NCATS Office of Communications.



Protocol #6713: A Natural History Study of Gangliosidosis and Other Hexosaminidase Deficiencies

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effectiveness of any therapies developed in the future; and (4) to better understand the neurological involvement in late-onset Tay–Sachs disease.

The study population includes any infantile, juvenile or adult patient with Tay–Sachs or Sandhoff disease, or GM1 gangliosidosis. The participation criterium for this study is having a gangliosidosis disease.

In this study, each individual affected by the infantile or juvenile forms of disease undergoes a baseline evaluation, and subsequent evaluations during their normal clinical visits, that include: (1) completion of neuropsychological and neurobehavioral assessments that measure fine and gross motor skills, visual tracking and attention, communication (verbal and non-verbal), and emotional and social behaviors; and (2) completion of quality-of-life and infant and toddler health questionnaires by participants' caregivers. The quality-of-life and infant and toddler health questionnaires were developed by Dr. Florian Eichler.

Because more is known about LOTS, the investigators formed the following hypotheses:

1. Patients with LOTS will show progressive, decreased cerebellar and frontal volumes relative to other brain structures (as suggested by previous studies).
2. Patients with LOTS will show a pattern of abnormality on neuropsychological testing consistent with cerebellar and frontal dysfunction. The investigators will determine if this pattern of abnormality is progressive.

To elucidate the central nervous system structural and functional abnormalities in LOTS disease, and to measure the changes over time in these participants, changes in brain volume will be measured using brain volumetric analysis in MRI examinations repeated over time. Neuropsychological changes will



be assessed by testing IQ, attention, and executive functions. The questionnaire developed by Dr. Eichler for LOTS patients will be used to assess quality-of-life and participant behavior over time. Also, if possible, investigators will record the precise nature of LOTS disease participants' genetic mutations.

The combination of using quantitative MRI and neuropsychological testing will be used to answer the following questions:

1. Can the cerebellar loss of volume be confirmed by volumetric analysis on MRI? Is this loss particularly found in the posterior lobes? Are other brain abnormalities revealed by volumetric analysis? Are there abnormalities of functional brain connections revealed by MRI?
2. Are the neuropsychological test data patterns consistent with previous research indicating executive, spatial, and memory difficulties? If so, are any of these functional abnormalities related to cerebellar volumes or Diffusion Tensor Imaging (DTI) results?
3. Is there a change over time in executive functions in LOTS disease? Is any such change associated with changes in brain volume seen on MRI?
4. Are there risk factors that may predispose LOTS disease patients to psychiatric or executive function problems (i.e. nature of genetic mutation, age of onset, or pre-existing vulnerabilities)?

To learn more details about LDN protocol number 6713, which is being continued by an extension study during the renewed NIH funding cycle, search for its ClinicalTrials.gov identifier number NCT00668187 at: <http://clinicaltrials.gov/ct2/search/index>.

Abstracts resulting from LDN protocol number 6713:

K. Bjoraker, J.B. Eisengart, P. Karachunski, G. Oz, C.B. Whitley, A natural history study of hexosaminidase deficiency. *Mol Genet Metab* 99(2) (2010) S11.

J.R. Utz, F.S. Eichler, R.S. Ziegler, B.M. Diethelm-Okita, R.L. LeDuc, C.B. Whitley, A natural history of hexosaminidase deficiency. *Mol Genet Metab* 102(2) (2011) S43.

B.M. Diethelm-Okita, J.R. Utz, F.S. Eichler, R.S. Ziegler, R.L. Leduc, C.B. Whitley, A natural history of hexosaminidase deficiency. *Mol Genet Metab* 105(2) (2012) S61-S62.

Central Nervous System Treatment for MPS II is the Focus of a New Development Agreement between Shire plc and ArmaGen Technologies, Inc.

ArmaGen, a privately-held biotechnology company focused on developing therapies to effectively treat diseases that cause severe neurological disorders, announced on July 23, 2014 that it has entered into a worldwide licensing and collaboration agreement with Shire plc to develop AGT-182, an investigational enzyme replacement therapy (ERT) for potential treatment of both the central nervous system (CNS) and somatic (body-related) manifestations of Hunter syndrome (MPS II). For more information about MPS II, read "Check Your Knowledge" in the first issue of 'Indications,' the December 2013 issue, which is downloadable from www.LysosomalDiseaseNetwork.org (see links on the upper-right area of the home page).

Previously, Shire researched, developed and commercialized the first treatment approved for Hunter syndrome. This was Elaprase, an ERT approved by the FDA in 2006. The new agreement with ArmaGen expands Shire's commitment to finding treatments for Hunter syndrome. This commitment also includes SHP-609, Shire's product currently being investigated to treat the CNS manifestations associated with Hunter syndrome. It is estimated that 2/3 of all MPS II patients will be affected with CNS disease; this translates into a prevalence of around 1,200 patients worldwide.

The collaboration between ArmaGen and Shire on AGT-182 will be managed by a joint steering committee, with representatives from both companies. ArmaGen will be responsible for conducting a Phase 1/2 study of AGT-182; it expects to initiate the trial before the end of 2014. Shire will be responsible for further clinical development, including Phase 3 trials,



registration and commercialization of AGT-182 worldwide.

Philip J. Vickers, Ph.D., Global Head of Research and Development at Shire, said "Our agreement with ArmaGen strengthens our long-standing commitment to the Hunter syndrome community to bring forward novel therapies that have the potential to dramatically redefine the treatment paradigm and address the most critical unmet needs. AGT-182 has the potential to be an important new therapy to our existing portfolio of Hunter syndrome programs. We plan to apply our proven ability to develop therapies for rare genetic diseases to progress AGT-182 as a potential treatment that offers hope to patients with Hunter syndrome and their families."

AGT-182 has received orphan drug designation from both the FDA and the EMA (European Medicines Agency). Using ArmaGen's proprietary technology, AGT-182 is designed to take advantage of the body's natural system for transporting products across the blood-brain barrier (BBB) by binding to the same receptor that delivers insulin to the brain. AGT-182 is engineered by the fusion of the replacement enzyme iduronate-2-sulfatase (IDS) with an antibody that is attracted to a receptor on the BBB. The IDS enzyme is designed to travel through the BBB while attached to that antibody.

Information for this article was provided by Shire plc and ArmaGen Technologies, Inc.

Improve Your Awareness of Important New Studies



Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)

An ongoing longitudinal study involving a treatment approach for gangliosidoses has been included as one of the new LDN protocols for the LDN's renewed NIH funding cycle. This study is entitled "Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)." The Principal Investigator of this study is Dr. Jeanine Utz, PharmD, a clinical pharmacotherapist and LDN researcher at the University of Minnesota Twin Cities campus. Co-investigators of this study are Dr.

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Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)

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Richard Ziegler and Dr. Kelly King, Dept. of Pediatric Neuropsychology at the University of Minnesota Twin Cities campus.

The Syner-G regimen is an enteral combination therapy using the commercially available treatment miglustat combined with a ketogenic diet. This study is a 5-year longitudinal treatment study. Data are collected during yearly evaluations and at completion of study. Investigators may choose to stop therapy at any time as clinically indicated for individual patients.

The primary objective of this study is overall survival of patients with infantile and juvenile gangliosidoses compared to survival data from previously reported natural history studies of infantile and juvenile gangliosidoses. The secondary objectives of this study are to evaluate the effect of Syner-G therapy on neurodevelopmental status and quality of life. An additional secondary objective is to explore potential serum and cerebrospinal fluid biomarkers of gangliosidosis disease that may be associated with disease severity and/or changes in disease status.

Change in neurodevelopmental abilities will be evaluated over the duration of the study and compared to available natural history data. This analysis will be conducted separately for patients with Tay–Sachs disease, Sandhoff disease and GM1 gangliosidosis, as well as the infantile and juvenile subtypes of these diseases. The primary neurocognitive functioning endpoints are age-equivalent scores of the Bayley Scales of Infant and Toddler Development for cognitive, expressive communication, receptive communication, fine motor skills and gross motor skills; and the Vineland Adaptive Behavior Scales. Participants' quality of life will be assessed using the following tools: Living Infantile Tay–Sachs Questionnaire for infantile gangliosidosis, and Living Juvenile Tay–Sachs Questionnaire for juvenile gangliosidosis.

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Meet the Principal Investigators



Chester B. Whitley, Ph.D., M.D., is Professor, Division of Genetics & Metabolism, Department of Pediatrics, University of Minnesota, Twin Cities campus. Dr. Whitley served as organizing chairperson for establishment of the Lysosomal Disease Network in 2004,



Chester B. Whitley, PhD, MD

and is its Principal Investigator. A lifetime career objective of his has been to develop treatments for lysosomal diseases. Following Ph.D. and M.D. training focused on lysosomal diseases, he joined the faculty at the University of Minnesota and began the seminal clinical trials of bone marrow transplantation for Hurler syndrome (1983) and other lysosomal diseases. He subsequently

accomplished the only human clinical trial of gene therapy for Hunter syndrome (USFDA BB-IND: #5370; Autologous Peripheral Blood Stem Cells for Hunter Syndrome Cultured Ex-Vivo with Anti-CD3 and Interleukin-2; Transduced L2SN Expressing IDS Gene, 1995), and has led an NIH-funded program project grant entitled “Gene Therapy for Metabolic Disorders” for more than 15 years. Clinically, Dr. Whitley has been involved in more than two dozen University-originated clinical trials, and served as local site Principal Investigator for dozens of industry-sponsored clinical trials of new drugs. His key role in the founding of the Lysosomal Disease Network has been an especially fruitful endeavor that is proving to have tremendous impact on moving-forward therapy for these conditions. Dr. Whitley is Principal Investigator of LDN protocol number 6713, entitled “A Natural History Study of Gangliosidosis and Other Hexosaminidase Deficiencies” (see page 4), and of LDN protocol number 6718, a pilot study entitled “Gene Therapy for Tay–Sachs Disease (Phase 1: Natural History Data Gather).” Following renewal of the LDN’s NIH funding, he will be the

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Meet the Principal Investigators

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Principal Investigator of the LDN continuation study entitled “Longitudinal Studies of Brain Structure and Function in MPS Disorders.”

Selected Chester B. Whitley Publications:

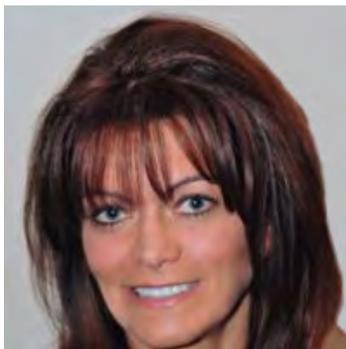
C.B. Whitley, N.K. Ramsay, J.H. Kersey, W. Krivit, Bone marrow transplantation for Hurler syndrome: assessment of metabolic correction. *Birth Defects Orig Artic Ser* 22(1) (1986) 7-24. PMID: 3083887.

S.E. Braun, E.L. Aronovich, R.A. Anderson, P.L. Crotty, R.S. McIvor, C.B. Whitley, Metabolic correction and cross-correction of mucopolysaccharidosis type II (Hunter syndrome) by retroviral-mediated gene transfer and expression of human iduronate-2-sulfatase. *Proc Natl Acad Sci USA* 90(24) (1993) 11830-11834. PMID: PMC48078.

L. Ou, T. Herzog, B.L. Koniar, R. Gunther, C.B. Whitley, High-dose enzyme replacement therapy in murine Hurler syndrome. *Mol Genet Metab* 111(2) (2014) 116-122. PMID: PMC4014311. [Available on 2/1/2015]



Jeanine R. Utz, PharmD, trained as a Lysosomal Disease Network Fellow from 2009-2011. Dr. Utz directs a post-doctoral PharmD fellowship program at the University of Minnesota College of Pharmacy, called the “Pharmacotherapy of Inherited Metabolic



Jeanine R. Utz, PharmD

Diseases PharmD Fellowship.” Following renewal of the LDN’s NIH funding, she will be the Principal Investigator of an LDN continuation study, an extension of current protocol number 6713, entitled “A Natural History Study of Gangliosidosis and Other Hexosaminidase Deficiencies.” She will also be the Principal Investigator of a new LDN study entitled “Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)” (see page 6).



Dr. Utz’s current research projects include studies of: 1) the natural history of the gangliosidoses; 2) classifying and managing infusion reactions (acute, delayed and biphasic infusion reactions) to intravenous enzyme replacement therapy for lysosomal diseases; 3) Syner-G, a combination enteral regimen for treatment of the gangliosidoses; 4) the impact of clinical pharmacotherapy services on clinical outcomes in inherited metabolic disorders, including lysosomal diseases and phenylketonuria (PKU); and 5) pharmacogenetics of tetrahydrobiopterin therapy for PKU.

Selected Jeanine R. Utz Publication:

C.B. Whitley, J.R. Utz, Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI): a single dose of galsulfase further reduces urine glycosaminoglycans after hematopoietic stem cell transplantation. *Mol Genet Metab* 101(4) (2010) 346-348. PMID: 20800524.

Synergistic Enteral Regimen for Treatment of the Gangliosidoses (Syner-G)

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Additionally, the following parameters will be recorded: changes in optic nerve atrophy and cherry red spot; changes in seizure frequency and severity; changes in cardiac health, including cardiac output; and changes in total brain volume, intracranial brain volume, and brain structures using semi-automated quantitative measurements applied to brain MRI.

To learn more details about Dr. Utz’s Syner-G study, which is actively recruiting participants, search for its ClinicalTrials.gov identifier number NCT02030015 at: <http://clinicaltrials.gov/ct2/search/index>.

Participants in Dr. Utz’s Syner-G study may also be participants in LDN Protocol #6713: A Natural History Study of Gangliosidosis and Other Hexosaminidase Deficiencies (see page 4). To learn more details about that ongoing study, which is also actively recruiting participants, search for its ClinicalTrials.gov identifier number NCT00668187.



Meet Our Patient Advocacy Groups

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diseases and to support affected individuals and families in leading fuller lives. NTSAD's goals are to:

- direct, fund and promote research to develop treatments and cures;
- provide comprehensive support services to affected families and individuals; and
- guide prevention, education, awareness and screening through effective grassroots collaborations with chapters and affiliates.

NTSAD History Highlights

In 1958 the first "International Symposium" convened, funded by NTSAD and chaired by Bruno W. Volk, M.D. that was exclusively devoted to discovering the cause of, and treatment for Tay–Sachs disease and other sphingolipidoses. In 1970, Dr. Michael Kaback, who retired from UCSD Medical Center in San Diego, conducted the first mass public screening in Maryland to identify Tay–Sachs disease carriers, funded in part by NTSAD. Tay–Sachs disease was thus established as the **first** genetic disease meeting the criteria for public prevention programs.

In 1971 the first "International Symposium on Sphingolipids, Sphingolipidoses and Allied Disorders" was held in Brooklyn, NY, under auspices of the NTSAD and the Isaac Albert Research Institute of the Kingsbrook Jewish Medical Center. In 1975 the first "International Conference on Tay–Sachs Disease: Screening and Prevention" was held, funded by NTSAD and the National Foundation of the March of Dimes. In 1992 NTSAD sponsored the first conference for individuals and families affected by **late-onset** Tay–Sachs disease. In 1996 NTSAD debuted on the World Wide Web. In 2001 NTSAD rededicated itself to funding cutting-edge scientific and medical research, and established the NTSAD Research Initiative to focus on funding innovative research for neurodegenerative diseases that affect the central nervous system. NTSAD focuses on funding promising research that may lead to other major grant support, and funding programs with the potential to reach clinical trials.



In 2002 NTSAD marked its 45th anniversary year as the oldest genetic disease organization in the nation by bringing together leaders of genetic disease communities for its first "Summit of the Allied Diseases." The meeting pulled together professionals in the field of rare diseases to discuss the ongoing work and challenges and to develop opportunities to collaborate. Members of professional groups such as the National Organization of Rare Disorders (NORD) and Genetic Alliance, researchers from universities and industry, and parents attended the summit.

NTSAD has organized numerous other educational meetings over the years, including a 2009 continuing medical education program: "Diagnosis, Management & Treatment of Progressive Neurological Disease from Infancy to Adult using Tay–Sachs Disease as a Model." Other NTSAD-organized Science Symposia include "New Topics in LSD Therapies" (2009) and "Mechanisms and Interventions in Childhood Neurodegeneration" (2011).

Leadership

Susan Kahn is the Executive Director of NTSAD. Sue joined NTSAD as Executive Director in September 2007. Sue first learned about NTSAD while working at Genzyme Genetics, where prior to NTSAD, she was Senior Director of Business Development and was responsible for strategy development, new product assessment, and technology licensing.



Susan R. Kahn
Executive Director
NTSAD

Sue earned an MBA from the Amos Tuck School of Business Administration at Dartmouth College, and a bachelor's degree in Applied Mathematics–Economics from Brown University. Sue is responsible for the strategic vision for NTSAD as well as day-to-day management. She has been focusing on NTSAD's research goals by updating the research strategy and collaborating with academia and the biotech industry. Most recently, Sue initiated NTSAD's Corporate Advisory Council, that will advise NTSAD on research partnering, priorities, and development of a clinical trial readiness infrastructure.

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Meet Our Patient Advocacy Groups

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The President of NTSAD is Shari Ungerleider, who has been involved with NTSAD since 1995 when her first child, Evan, was diagnosed with Tay–Sachs disease. Evan passed away in 1998. Shari and her husband, Jeff, have three other children. Having a child with a rare disease made her recognize the importance of raising awareness of these diseases and of helping to fund research. Through NTSAD Shari has become very involved in raising public awareness and providing education about carrier screening. She is also passionate about research and family support services for other families.



Shari Ungerleider
President, NTSAD

NTSAD Programs



Some NTSAD 2014 Peer Support Group (PSG) members

NTSAD's confidential family support network extends worldwide, with over 500 member families through its Peer Support Group (PSG). Member families and individuals regularly share their knowledge about home care, medical obstacles, grief and caring for a loved one with a rare genetic disease. Other

services available to PSG members include the Annual Family Conference, quarterly newsletters and monthly e-newsletters, and materials and support for fundraising and awareness events.

The Annual Family Conference, held every spring since 1979, is the cornerstone of the NTSAD family services program, and brings together these families, affected adults, healthy siblings, caregivers, and research and medical professionals. It provides over 200 parents, grandparents, affected children, healthy siblings, affected adults and their families the unique opportunity to gather with people that truly understand; learn about latest research and symptom management approaches; and discuss other important topics. The primary goals of the conference are to empower, support and connect families coping with Tay–Sachs, Sandhoff, Canavan or GM1 gangliosidosis diseases. A "Helping Hand Grant Program" assists families with financial need to attend the annual conference. Scholarships range in size from covering one night at the hotel to covering hotel, conference registration and travel expenses for the entire family. Each grant application is considered on an individual basis. Priority is given to newly-diagnosed families, families that have not attended before, and families that have lost their loved one in the past year.

Another NTSAD program, entitled "Benton's Family Assistance Fund", provides grants to qualified applicants to provide financial assistance to families and affected individuals to purchase items and services that promote comfort, ease, and quality-of-life for their loved ones. To qualify, applicants must be NTSAD Peer Support Group members, or a family member taking care of an affected child, or an affected adult or their caregiver. Ian and Marie Auerbach established Benton's Family Assistance Fund within NTSAD to honor their son, Benton, who passed away from Tay–Sachs disease in January 2012, at the age of 3.

NTSAD advocates for families and persons of all ages with disabilities on an individual, state and national level on issues such as off-label drug use, medical foods such as high-caloric formulas, compassionate allowances from the Social Security Administration, health insurance coverage and government (supplemental) funding. NTSAD also lobbies with the mem-



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Check Your Knowledge of Lysosomal Diseases



How well do you know the gangliosidoses?

By Evelyn S. Redtree, M.S. and Jeanine R. Utz, PharmD

The gangliosidosis diseases are a group of inborn errors of ganglioside metabolism resulting from deficiency of specific enzyme activity, leading to the pathologic progressive accumulation of gangliosides in tissues. Central nervous system involvement is the most prominent effect. The gangliosidosis diseases include GM1 gangliosidosis and GM2 gangliosidosis (Tay–Sachs disease, Sandhoff disease) and have various ages of onset, rates of progression and mortality. Both GM1 gangliosidosis and GM2 gangliosidosis are typically described as having one of three phenotypes, based upon onset of symptoms: infantile onset (within the first year of life), juvenile onset (during early childhood) or late onset (onset often occurring between the second and fourth decade of life).

The primary clinical manifestations of these conditions are neurodegenerative in nature, owing to the progressive accumulation of gangliosides in the brain, where gangliosides are a major component of the central nervous system structure and function.

GM1 gangliosidosis is caused by mutations of the GLB1 gene (cytogenetic location 3p22.3), resulting in deficiency of β -galactosidase and subsequent accumulation of GM1 ganglioside substrates in lysosomes.

The GM2 gangliosidoses are caused by mutations of genes encoding the α and β subunits of β -hexosaminidase. These genes are called HEXA (cytogenetic location 15q23-q24) and HEXB (cytogenetic location 5q13.3), respectively. Hexosaminidase A activity is deficient in Tay–Sachs disease, whereas both hexosaminidase A and hexosaminidase B activity is deficient in Sandhoff disease. Clinically, Sandhoff disease is indistinguishable from Tay–Sachs disease.

The AB variant of Tay–Sachs disease (mutation cytogenetic location 5q33.1), also known as hexosami-

dase activator deficiency, GM2 activator deficiency, or GM2 gangliosidosis AB variant, exhibits a phenotype very similar to that of classic Tay–Sachs disease. GM2-gangliosidosis AB variant is characterized by normal hexosaminidase A (HEXA) and hexosaminidase B (HEXB), but the inability to form a functional GM2 activator complex. This results in the inability of hexosaminidase A enzyme to become activated.

Incidence

GM1 Gangliosidoses

Worldwide incidence of GM1 gangliosidoses is estimated to be 1:100,000 to 200,000. GM1 gangliosidoses occur in all ethnicities and races. Type I is reported more frequently than the other forms of this condition. High prevalence has been found in Malta and Brazil, and in the Cypriot and Roma populations. Most individuals with type III are of Japanese descent.

GM2 Gangliosidoses

In the general world population, the incidence of GM2 gangliosidoses is about 1:320,000. Due to what is generally accepted to be founder effects, approximately 1:27 Ashkenazi Jews or persons of Eastern European descent is a *carrier* of a mutation that results in this disease. Even though there is a high incidence of this disease among people of Eastern European and Ashkenazi Jewish descent, Tay–Sachs disease has been reported in children of nearly all ethnic, racial, and religious populations. French Canadians of the eastern St. Lawrence River Valley area of Quebec, Cajuns from Louisiana, and the Old Order Amish in Pennsylvania have been found to carry GM2 gangliosidoses mutations with frequencies equal to, or even greater than, those seen in the Ashkenazi Jewish population. In contrast, the *carrier* rate for other non-Jewish individuals is estimated to be 1:300.

Presentation

Infantile Phenotypes of GM1 and GM2 Gangliosidoses

The infantile forms of GM1 gangliosidosis and GM2 gangliosidosis present with rapid psychomotor deterioration, usually noted within 6 months of birth, and progresses rapidly to severe neurological impairment within the first year of life, with death often occurring



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Check Your Knowledge of Lysosomal Diseases



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occurring by 3 years of age. Symptoms include pronounced hypotonia, dysphagia, seizures, and cognitive impairment. A typical fundoscopic finding is the cherry-red spot seen in the macular area, resulting from development of grayish-white coloration in the remainder of the retina due to presence of lipid-laden ganglion cells. An early and persistent extension-response to sound (startle reaction) is useful for recognizing Tay–Sachs disease.

Patients with GM1 gangliosidosis may present with skeletal dysplasia including kyphosis. A subset of GM1 gangliosidosis type I patients also present with cardiovascular involvement. Their signs may include dilated cardiomyopathy, hypertrophic cardiomyopathy, congestive heart failure, valvular heart disease, and possibly coronary artery occlusion by atherosclerotic plaques containing ballooned cells.

Juvenile Phenotypes of GM1 and GM2 Gangliosidoses

The juvenile forms of GM1 and GM2 gangliosidosis have a later onset compared to the infantile forms, with onset of notable symptoms commonly occurring between the age of 1 year and 5–6 years of life. Death often occurs between 10 to 15 years of age. Disease features of the juvenile forms include psychomotor deterioration including ataxia, hypotonia, progressing spastic quadriplegia, seizure disorders and spasticity; with development of dysarthria, dysphagia, and optic atrophy. Hepatomegaly and macular cherry-red spots are often absent in the juvenile forms.

Late-Onset Phenotypes of GM1 and GM2 Gangliosidoses

The late-onset or adult/chronic forms of the GM1 and GM2 gangliosidoses often have symptoms first noted between the second and fourth decade of life. Some patients present with only focal neurologic signs, such as dystonia, dysarthria, or gait disturbance; while other patients have more severe in-

volvement, with muscle atrophy, mild diffuse cerebral atrophy, extrapyramidal signs and mental retardation.

Late-onset Tay–Sachs disease, also known as LOTS, or adult-onset Tay–Sachs disease, is frequently misdiagnosed, as, for example, Friedreich’s ataxia, multiple sclerosis, or amyotrophic lateral sclerosis. It is characterized by unsteadiness of gait and progressive neurological deterioration, resulting in loss of ambulation. Signs of late-onset Tay–Sachs disease include dysarthria, dysphagia, spasticity, progressive cognitive decline, and psychiatric illness including psychosis.

Late-onset GM1 gangliosidosis can present with localized skeletal involvement, possibly including hypoplastic acetabulae, flat femoral heads, flared iliac wings, mild platyspondyly, mild anterior beaking of lumbar vertebrae, kyphosis, scoliosis, and/or short stature.

Inheritance

All gangliosidoses are inherited in an autosomal recessive manner. In other words, the disease results from the inheritance of two mutations in the responsible gene—one mutation from each parent. The gangliosidoses autosomal recessive inheritance can be complex, with multiple alleles and compounds. That is, affected persons may have two differing mutations, one from each parent, that each inhibit specific enzyme activity. In the case of the GM1 gangliosidoses, more than 165 different causative mutations have been identified so far. In the case of the GM2 gangliosidoses, more than 100 different causative mutations have been identified. These mutations have included single base insertions and deletions, splice phase mutations, missense mutations, and other more complex patterns. Each of these mutations alters the gene’s protein product (i.e. the enzyme), sometimes severely inhibiting its function.

Prevention, Not Cures

There are no cures for the gangliosidoses. Rather, prevention is key. Population screening was initiated in 1970 for Jewish individuals of reproductive age, and is recommended in published guidelines of the American College of Obstetrics and Gynecology (visit: http://www.acog.org/Resources_And_Publications/Commitment).



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tee_Opinions/Committee_on_Genetics/Screening_for_Tay_-_Sachs_Disease). Such genetic screening programs educate couples regarding their carrier status and the associated risks. Since 1970, anonymous genetic screening, genetic counseling and prenatal genetic analysis have reduced the incidence of Tay–Sachs disease among the Ashkenazi Jewish population by more than 90 percent. Until medical research succeeds in developing cures for the gangliosidoses, prevention remains critically important for reducing the burden of these diseases upon humanity.

Funding Opportunities in the NIH “New Therapeutic Uses” Program

In May 2012, NIH’s National Center for Advancing Translational Sciences (NCATS) launched the “Discovering New Therapeutic Uses for Existing Molecules” collaborative program. Therapeutic drug development is a costly, complex and time-consuming process. In the U.S., the average length of time from therapeutic-target discovery to approval of a new drug is about 14 years. The failure rate during this process *exceeds* 95 percent, and the cost per successful drug can be \$2 billion or more. This high drug-development failure rate means there are many existing, partially-developed therapeutic candidates (“agents”) that might be repurposed for use in a new disease indication. Pairing promising partially-developed agents from pharmaceutical companies with the best new ideas from academic researchers might produce new treatments much more quickly than starting from scratch.

The “New Therapeutic Uses” program, as it is more commonly known, helps re-engineer the research pipeline using this innovative strategy to identify new uses for agents that have undergone significant research and development by industry, including safety testing in humans. By participating in this

program, scientists nationwide have a strong starting point to contribute their unique expertise and accelerate the pace of therapeutic drug development.

An hour-long video made on May 3, 2012 when Health and Human Services Secretary Kathleen Sibelius announced the creation of the New Therapeutic Uses program, has been made available by the National Press Club, and can be found on the Web page at: <http://www.ncats.nih.gov/news-and-events/media/multimedia/vid-programs/programs.html>.

In May 2014, NCATS issued four funding opportunities and provided information about partially developed agents. Now, for the first time in the program, the participating pharmaceutical companies have made available agents that are suitable for exploring pediatric indications. A table showing the available agents is located near the bottom of the Web page at: <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory2014.html>.

In May 2014, NCATS issued the following four funding announcements:

PAR-14-213: Pre-application for the NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules (X02)

PAR-14-212: Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules (UH2/UH3)

PAR-14-211: Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules (UH3)

PAR-14-210: Limited Competition for NIH-Industry Program: Discovering Pediatric New Therapeutic Uses for Existing Molecules (UH2/UH3)

For detailed information about each of these four opportunities, click on hyperlinks in each funding announcement on: <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/funding.html>.

Source information for this article was provided by the NIH’s National Center for Advancing Translational Sciences (NCATS).



Meet Our Patient Advocacy Groups

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bers of the Rare Disease Congressional Caucus. NTSAD works closely with NORD to support legislative issues important to the NTSAD family. In recent years the NTSAD has successfully helped to advocate for the passage of the Genetic Non-Discrimination Act (GINA) that protects against discrimination based on genetic information. NTSAD also supported legislation that *requires* public access to research funded by federal funds. Upon request, NTSAD will provide free brochures and educational materials for congressional visits. NTSAD participates in International Rare Disease Day in collaboration with Global Genes Project and NORD by representing the rare disease community at events on the state and industry level. NTSAD encourages families to attend the events the Rare Disease Legislative Advocates (<http://rareadvocates.org/>) organize on Capitol Hill every year.

Leading the Effort to Fund Productive Research

NTSAD's goals are to direct, fund and promote research to develop treatments and cures. NTSAD launched its Research Initiative in 2002 to fund innovative research for neurodegenerative diseases that affect the central nervous system. Funding for the grants comes from gifts to NTSAD's Research Initiative from NTSAD's chapters and affiliates, as well as donations and fundraising events. Forty-one grants totaling \$3.0 million have been awarded, leading to NIH grants of more than \$10 million toward finding a cure. These grants have supported rare genetic disease research focusing on Tay–Sachs, Sandhoff, GM1 gangliosidosis, Canavan, Batten, and Krabbe diseases. The projects funded include gene therapy, stem cell treatment and enzyme enhancement, as well as identifying biomarkers and undertaking natural history studies. Grants may be made in collaboration with partners such as the NIH and other patient advocacy groups for related genetic diseases.

All grant proposals are reviewed and evaluated by members of the NTSAD Scientific Advisory Committee and other qualified scientists. Then the Research Initiative Committee of the NTSAD Board of Directors



reviews the expert evaluations and makes the final award selection. The Research Initiative Committee is made up of dedicated people directly affected by these diseases.

Once the grants are awarded, the researcher and their institution sign an agreement that they will agree to the terms and conditions in the NTSAD's Research Initiative Grant Policies. These policies include intellectual property clauses and related terms to protect the interests of families. The policies also outline the system for making the grant payments in installments, following approved research-progress reports. This process ensures that the highest quality science, and projects with the most meaningful outcomes are awarded. In addition, the process holds the researchers accountable for following through appropriately with their proposed project.

The Tay–Sachs Gene Therapy (TSGT) Consortium was formed in 2007 with the goal of initiating a gene therapy clinical trial for Tay–Sachs disease and Sandhoff disease. The TSGT Consortium is an international collaborative group of scientists committed to translating current results from animal experiments into a human clinical trial. Through the Research Initiative, NTSAD continues to support the TSGT Consortium in their animal-model studies and vector development, hopefully leading to human clinical studies. In August 2009 the National Institutes of Health awarded a \$3.5 million grant to the Tay–Sachs Gene Therapy Consortium to continue their research.

The TSGT Consortium consists of physicians and scientists from five institutions who are experienced in gene therapy and basic disease research: Auburn University, Boston College, Cambridge University (U.K.), University of Massachusetts Medical School, and Massachusetts General Hospital/Harvard University. The TSGT Consortium is led by Miguel Sena Esteves, PhD, an Associate Professor in the Department of Neurology and Gene Therapy Center at the University of Massachusetts Medical School. Last year, the FDA granted orphan drug designation for Tay–Sachs and Sandhoff gene therapy to facilitate development of these potential therapies. NTSAD was the sponsor for the applications. Promising therapeutic results have been obtained in several animal models of Tay–Sachs and Sandhoff disease, as well as GM1 gangliosidosis.

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Meet Our Patient Advocacy Groups

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They hope to complete the pre-clinical studies during 2014.

Getting the Message Out: Genetic Screening is Key

Until a cure is found, education, coupled with carrier screening, is the most effective tool in the campaign to prevent Tay–Sachs, Canavan and related diseases. As part of its educational and awareness program, NTSAD helps couples and individuals navigate the complicated world of genetic screening. Anyone can be a carrier, regardless of background, although Ashkenazi Jews, French-Canadians, Louisiana Cajuns and Irish-Americans are at a higher risk for being Tay–Sachs carriers. NTSAD offers educational and awareness programs directly, as well as through collaborations with NTSAD local chapters, affiliates and other community partners. These partners include the Jewish Genetic Disease Consortium, the Victor Centers for Jewish Genetic Diseases, NTSAD's Delaware Valley Chapter, and the Mathew Forbes Romer Foundation, a south Florida affiliate of NTSAD.

Educational outreach includes forms such as: live speakers available to present in front of groups; free videos appropriate for a general lay audience of teenagers or adults; free videos targeted to specific at-risk groups; videos targeted to physicians; and brochures, fact sheets, family-resource guides, patient home-care guides, Web-based information, television and radio public service announcements.

The NTSAD-produced film, *Parenting a Child with Life-Limiting Illness*, was launched in 2013 (<http://www.ntsad.org/index.php/infantile-a-juvenile-support/parenting-a-child-with-life-limiting-illness>). It was made possible thanks to a Patient Advocacy Leadership (PAL) Award Innovation Grant from Genzyme. It was created to lessen the feelings of isolation that any newly-diagnosed family experiences. NTSAD also provides free training for Rabbis and other community leaders and educators, to equip them to make public educational presentations stressing the importance of genetic screening/prenatal testing for these diseases.



The NTSAD International Tay–Sachs Carrier Testing Quality Control Program is a voluntary laboratory proficiency ascertainment program for Tay–Sachs enzyme testing. Enzyme testing continues to be the gold standard for identifying Tay–Sachs carriers. The program evaluates laboratory performance of Tay–Sachs biochemical carrier screening in serum and leukocytes. This program was founded and administered by Dr. Mike Kaback at the University of California-San Diego for its first 25 years, and is now being run in the lab of Dr. Mimi Blitzer and Dr. Erin Strovel at the University of Maryland.

More information about the NTSAD is available at their Web site, <http://www.ntsad.org/>. If you are interested in signing up for any e-news from NTSAD, including funding announcements, please send an email to: diana@ntsad.org; or sign-up on their Web site.

Find More Information at These Web Sites:

National Tay–Sachs & Allied Disease Association of Delaware Valley (NTSAD-DV)
<http://www.tay-sachs.org/>

NTSAD New York Area Chapter
<http://www.ntsad-ny.org/index.html>

Cameron and Hayden Lord Foundation
<http://lordfoundation.org/>

Chicago Center for Jewish Genetics
<https://www.jewishgenetics.org/>

Cure Tay–Sachs Foundation
<http://www.curetay-sachs.org/>

The Jewish Genetic Disease Consortium (JGDC)
<http://www.jewishgeneticdiseases.org/>

Mathew Forbes Romer Foundation,
based in South Florida
<http://www.mfrfoundation.org/index.php>

The Victor Center for Jewish Genetic Diseases
Philadelphia, PA
<http://www.victorcenters.org/>





Shoulders of Giants

Death of John A. Barranger, co-founder of Lysosomal Disease Network

With great sadness the LDN marks the passing of John Arthur Barranger, Ph.D., M.D., co-founder of the Lysosomal Disease Network in 2004, and pioneer who led the way in developing the first enzyme replacement therapy (ERT) for a lysosomal disease, who died at his home in Pittsburgh, PA on May 25, 2014. Dr. Barranger dedicated his career to improving the quality of life for patients with lysosomal diseases; his efforts positively impacted thousands of patients.

Dr. Barranger earned his Ph.D. and M.D. at the University of Southern California. He then completed an internship and residency in pediatrics at the University of Minnesota in 1976. After leaving Minne-



John Arthur Barranger, Ph.D., M.D.

sota, as an NIH Fellow in Genetics, from 1976 to 1978 Dr. Barranger served in the Clinical Investigations and Therapeutics Section, Developmental and Metabolic Neurology Branch (DMNB), at the NIH's National Institute of Neurological and Communicative Disorders and Stroke. He ultimately became Chief of the Molecular and Medical Genetics Section of the DMNB.

Dr. Barranger served for many years as professor in the Departments of Human Genetics, Molecular Genetics and Biochemistry, and Pediatrics at the University of Pittsburgh, where he developed and directed the Human Gene Therapy Applications Laboratory, the Center for the Study and Treatment of Jewish Genetic Diseases, and the Comprehensive Gaucher Disease Treatment Center. He concurrently



co-directed the Human Gene Therapy Center, and served as Medical Director of the Molecular Medicine Institute. His research interests included biochemical and molecular genetics, enzyme therapy, gene transfer, and models of genetic disease. Dr. Barranger published more than 450 papers and abstracts.

As a result of his investigation of the structure of glucocerebrosidase and receptors on macrophages, Dr. Barranger pioneered successful enzyme replacement therapy for Gaucher disease, the first ERT, which received U.S. Food and Drug Administration approval in 1991. This achievement led directly to the birth of a biotechnology industry, first represented by Genzyme Corporation.

Included among Dr. Barranger's honors are the March of Dimes Health Career Award, the United States Public Health Service Commendation Medal, the Arthur S. Flemming Award that recognizes outstanding Federal employees, and the Scientific Achievement Award of the National Gaucher Foundation. He served as Medical Advisory Board Member as a member of the National Gaucher Foundation. How fortunate the lysosomal disease community is, to have had such a person devote his professional life to its needs!



Bright Ideas

The Caregiver Action Network, a Washington D.C.-based non-profit organization dedicated to supporting family-based caregivers across all medical conditions, has launched a new Web site specifically for rare disease caregivers. The new site is worth exploring! Visit: <http://www.rarecaregivers.org/>

The Global Genes Project has a Web page providing information about sources of financial aid for families caring for seriously-ill family members. It may contain funding sources with which you are unfamiliar! Carefully read it at: http://globalgenes.org/toolkit_life-limiting_1c/

Calendar of Upcoming Events



Association for Glycogen Storage Disease 36th Annual Family/Medical Conference, September 19 - 20, 2014 in Dearborn, Michigan, USA at Doubletree by Hilton Hotel Detroit-Dearborn, 5801 Southfield Expressway, Detroit, MI, 48228. Visit: <http://www.agsdus.org/html/2014conference.html>

WORLD Fair (a one-day symposium), Saturday Sept. 20, 2014, at Hilton Minneapolis/St. Paul/Mall of America, 3800 American Blvd. E., Bloomington, MN 55425. Email or phone your RSVP: (763) 424-7983 or rsvp@WORLDsymposia.com

American Society of Human Genetics 64th Annual Meeting, October 18 - 22, 2014 in San Diego, California, USA. For more information, visit: <http://www.ashg.org/2014meeting/>

"360° Lysosome: from structure to genomics, from function to disease," October 23 - 28, 2014 in Izmir, Turkey. Course organizers/coordinators: Eser Y. Sozmen, M.D., Ph.D. and Michael Przybylski, Ph.D. For more information, visit: <http://www.febs-lysosome.org/>

Imagine & Believe Gala, the 7th Annual Boston Benefit for NTSAD, Thurs. evening Nov. 13, 2014 at the Royal Sonesta Hotel in Cambridge, Massachusetts. The NTSAD will honor Stephen C. Groft, former Director of the Office of Rare Diseases Research at NIH. For more information, contact Joan Lawrence, NTSAD Director of Development, at joan@ntsad.org, or call Joan at (617) 277-4463, or visit: <http://www.ntsad.org/index.php/resources/news/650-2014-imagine-believe-boston-benefit>

National MPS Society Annual National Family Conference, December 18 - 21, 2014 at Disney's Contemporary Resort in Orlando, FL, USA. Visit: https://mpssociety.org/event-registration/?regevent_action=register&event_id=147

Lysosomal Disease Network's 11th Annual *WORLDSymposium*[™], February 9 - 12, 2015 at the Hyatt Regency Orlando Hotel in Orlando, Florida. Abstract submission deadline is 11:59 pm CST, October 1, 2014. Visit: www.worldsymposia.org

Fabry Support & Information Group's 2015 FSIG Expert Fabry Conference, February 13 - 15, 2015 in Orlando, Florida. Details will become available as they are finalized. Visit: <http://www.fabry.org/FSIG.nsf/Pages2/HomePage>

2015 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, March 24 - 28, 2015 at the Salt Palace Convention Center in Salt Lake City, Utah. Visit: <http://ww4.aievolution.com/acm1501/>



Small molecule RNA Interference (RNAi) Biochemistry Data Made Available by NIH

RNA interference (RNAi) is a natural cellular process that can stop specific proteins from being coded, by silencing the genes that produce them. Cells use this process to control the activity of specific genes. Its discovery led to the awarding of the 2006 Nobel Prize in Physiology or Medicine to Andrew Z. Fire and Craig C. Mello. Gene silencing through RNAi has emerged as a powerful tool for researching gene function. High-throughput RNAi screens have illuminated a variety of biological processes, ranging from genes that affect the activity of therapeutic agents, to novel components of signaling pathways. For example, on Nov. 25, 2013 NIH announced that a team of NIH scientists led by Richard Youle, Ph.D. at NINDS and Scott Martin, Ph.D. at NCATS had used RNAi technology to identify dozens of genes that may represent new therapeutic drug targets for treating Parkinson's disease. The research was published online in *Nature*: <http://www.nature.com/nature/journal/v504/n7479/full/nature.12748.html>.

Now, data on the biochemistry of small interfering RNA (siRNA) molecules is publicly available. NIH announced on Dec. 11, 2013 that these data now are accessible to researchers worldwide. NCATS collaborated with Life Technologies Corp. of Carlsbad, California, owner of the siRNA information, to make it available to all researchers. NIH has established a state-of-the-art RNAi screening facility that accepts proposals from **any** NIH researcher. The staff at this facility, administered by the NCATS Division of Pre-Clinical Innovation, assist investigators with all stages of project planning and execution, beginning with assay development, through genome-wide siRNA screens, informatics/pathway analysis, and rigorous follow-up. Genome-wide siRNA screens for humans and mice are available. For more information about this powerful research tool opportunity, and for valuable hyperlinks, visit: <http://www.nih.gov/news/health/dec2013/ncats-11.htm>.

✓ To learn more about small molecule RNAi and gene silencing, *Nature* has a spectacular educational slideshow and video animation available at: <http://www.nature.com/nrg/multimedia/rnai/animation/index.html>.

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Indications[™]

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Content development, writing, editing,
design and layout: Evelyn Redtree, M.S.
LDNed@umn.edu