Indications™

Newsletter of The Lysosomal Disease Network™

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The LDN Awards the 2015 LDN Fellowship

Every year, the Lysosomal Disease Network (LDN) awards two $50,000 Fellowships to promising young researchers working on projects that can impact clinical care of patients with lysosomal diseases. One LDN Fellowship is located at the University of Minnesota, where the LDN is headquartered; the other is located outside of that university. The awardee of the 2015 extramural LDN Fellowship submitted a highly detailed research goal and plan, along with other NIH-required documents, and competed against nine other high-quality applications. The LDN expresses its gratitude to all the gifted scientists who competed for this 2015 award.

The 2015 LDN Fellowship is awarded to Dr. Mari Mori at Duke University. Dr. Mori's mentor during this research project is Dr. Priya Kishnani. The LDN Education and Training Committee was especially impressed by the scientific quality of the winning project, the favorable environment in which it will be conducted (based on the training and mentoring plan), and the potential for this project to satisfy an unmet need in Pompe disease through its proposal

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In This Issue. . .

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 . . .

The Leukodystrophy Alliance™

http://leukodystrophyalliance.org/

During May 2011, eight leukodystrophy foundations gathered for the first time in Buffalo, NY. The primary objective of this exploratory meeting was to determine if organizing an alliance and sharing resources would add value and strength to the leukodystrophy community at large. It was determined that the advantages of an alliance would be great, and that these foundations *should* form an organization. In follow-up meetings bylaws were created and the Leukodystrophy Alliance™ ("LA") was formed.

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The Lysosomal Disease Network (U54NS065768) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and 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.

Meet Our Patient Advocacy Groups

The Leukodystrophy Alliance

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The vision of the Leukodystrophy Alliance is that one day there will be a timely diagnosis and an accessible, effective therapy for everyone with a leukodystrophy. The mission of the Leukodystrophy Alliance is to leverage the strengths, resources, and efforts of an alliance of leukodystrophy support organizations. Together the alliance works to improve the quality of life for those living with leukodystrophy, while accelerating the development of, and improving access to, viable therapies.

Member organizations to date are:

1. **Australasian Leukodystrophy Foundation** (Australasian region) visit: http://australasianleukodystrophyfoundation.com/
2. **Bethanys Hope Foundation** (Canada) for metachromatic leukodystrophy; visit: http://bethanyshope.org/
3. **CADASIL Together We Have Hope** / **CADASIL Foundation** for cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; visit: http://www.cadasilfoundation.org/index.html
4. **Hunter's Hope Foundation**, for Krabbe disease; (see May 2014 issue of "**Indications**"); visit: http://www.huntershope.org/site/PageServer
5. **MLD Foundation**, for metachromatic leukodystrophy; visit: http://mldfoundation.org/
6. **Stop ALD Foundation**, for adrenoleukodystrophy; visit: http://www.stopald.org/
7. **The M.O.R.G.A.N. Project**, for support of parents caring for their children with special health care needs; visit: http://www.themorganproject.org/
8. **The Myelin Project**, for adrenoleukodystrophy and adrenomyeloneuropathy; visit: http://myelin.org/home.html
9. **The PMD Foundation**, for Pelizaeus Merzbacher disease; visit: http://pmdfoundation.org/
10. **The United Leukodystrophy Foundation**, for multiple leukodystrophies; visit: http://ulf.org/

A subset of members of the Leukodystrophy Alliance paused for a photo during a gathering in London, Ontario, Canada. From left, standing are Dr. Tony Rupar, Scientist, Division of Genetics & Development, Children's Health Research Institute in London, Ontario, Canada, who is also Associate Professor, Departments of Biochemistry and Paediatrics, Schulich School of Medicine & Dentistry, Western University; and is also Chair, Division of Clinical Biochemistry, Department of Biochemistry, Western University; and is also Director, Biochemical Genetics Laboratory, London Health Sciences Centre; all located in London, Ontario, Canada; next are Kristen Malfara for the M.O.R.G.A.N. Project; Andrea Moran and Jacque Waggoner for Hunter's Hope Foundation; Jeff Leonard for The PMD Foundation; Larry Chapman for The Myelin Project; and David McIntyre for Bethanys Hope Foundation. Sitting are Lindey McIntyre (left) for Bethanys Hope Foundation; and Patti Chapman for The Myelin Project.

Leukodystrophy Alliance Executive Committee:
President: Jacque Waggoner (Hunter's Hope Foundation, CEO)
Vice President: Ryan Gauss (Bethanys Hope Foundation, Chairman of Board)
Secretary: Patti Chapman (The Myelin Project, President and Board Chairwoman)

Still in the earliest phase of its existence, the LA is currently focusing on aiding the efforts of its member

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Leukodystrophy Care Network™ Seeks to Facilitate, Found and Coordinate Leukodystrophy Care Centers Throughout North America

Hunter's Hope Foundation (see May 2014 "**Indications**") is currently organizing and establishing the Leukodystrophy Care Network ("LCN"). Its mission is to leverage resources to enhance medical care in order to improve the quality of life of those affected with any of the leukodystrophy diseases. The vision driving the establishment of the Leukodystrophy Care Network is to create a world-renowned LCN across the United States, Canada and eventually the world, to provide innovative patient therapies, treatment options, expert care, and information for families affected by the leukodystrophy diseases. Leukodystrophy care centers ("LCC") will be financially self-sustaining, yet collaborative, and networked to ensure that the highest quality care is available for all leukodystrophy patients today, and for generations to come.

The LCN Advisory Committee advises regarding the planning, execution and continuous improvement of the LCN. The LCN Advisory Committee will administer a peer-reviewed protocol to identify and qualify medical professionals and leukodystrophy care centers throughout the United States and Canada. The LCN Advisory Committee will also define the data collection requirements, supported by an infrastructure for standardized data collection, for research to improve mulidisciplinary symptomatic care. It will collaborate with clinical research investigators, ensuring they have resources needed to further their work in finding new treatments. Additionally, it will educate patients and their families on emerging experimental therapies, and facilitate their access to participation in clinical trials.

The LCN Oversight committee, a subcommittee of the LCN, will monitor LCCs for adherence to requirements by conducting peer reviews. The LCN's network of leukodystrophy care centers will be administered through a coordinating center, which will also serve as a fully functioning LCC. Stay tuned for future developments with this exciting and bold endeavor!

Meet Our Patient Advocacy Groups

The Leukodystrophy Alliance

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Foundations to achieve newborn screening for all of the leukodystrophies for which screening tests exist, in each state or province where the Foundations are particularly active. The LA is also a very active member of GLIA (Global Leukodystrophy Initiative), which is a new organization focusing on leukodystrophy clinical care and research (see below). GLIA members meet face-to-face a couple of times each year, and meet quarterly via conference call. The Leukodystrophy Alliance has provided financial support for some of the GLIA face-to-face meetings.

For more information about the Leukodystrophy Alliance, please contact Jacque Waggoner (jacque@huntershope.org).

Global Leukodystrophy Initiative Attracts Global Leaders in Leukodystrophy Care and Research

Adeline Vanderver, M.D. (a neurologist at Children's National Research Center, Washington, DC) has recently organized a cooperative leukodystrophy research group called the Global Leukodystrophy Initiative ("GLIA") consisting of investigators from a number of institutions in the U.S. and abroad, and leukodystrophy patient advocacy group representatives. The Leukodystrophy Alliance is one of the patient advocacy groups participating in GLIA. Some other participants attending GLIA meetings include high-level officials from National Institute of Neurological Disorders and Stroke (NINDS), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Newborn Screening Translational Research Network (NBSTRN), National Organization for Rare Disorders (NORD), and numerous neurologists. Still in its early developmental stage, GLIA plans to develop shared diagnostic approaches for leukodystrophy patients, and conduct research projects across multiple leukodystrophy centers.

For more information, visit: http://theglia.org/

LDN Research *Matters*

Pilot Project 4: Long Term Follow Up for Krabbe Disease

By Evelyn S. Redtree, M.S. and Thomas J. Langan, M.D.

During the new funding cycle of the Lysosomal Disease Network, several pilot projects are being funded. (See page 14 for more information.) One of these pilot projects is "Pilot Project 4: Long Term Follow Up for Krabbe Disease." Pilot Project 4 is led by Thomas J. Langan, M.D., and is co-funded by Hunter's Hope Foundation. Dr. Langan is Clinical Research Director, Hunter James Kelly Research Institute in Buffalo, New York.

The hypothesis underlying this Pilot Project is that, as part of the known phenotypic variability of Krabbe disease, children with positive newborn screens for this condition will exhibit distinct developmental outcomes, which can be measured by standardized phone interview protocols. Further, it is hypothesized that, as part of the known phenotypic variability of Krabbe disease, children with positive newborn screens for this condition will exhibit distinct functional outcomes, which can be measured by standardized phone interview protocols.

The primary aims of this Pilot Project are: (1) using phone-based interviews, researchers will assess long-term developmental outcomes in children with positive newborn screens for Krabbe disease; and (2) using phone-based interviews, researchers will assess long-term functional outcomes in children with positive newborn screens for Krabbe disease. The rationale for this study is based on experience with a centralized phone interview technique, which has proven successful in infants with brain tumors in a national Children's Oncology Group study (Msall, 2010).

The purported incidence of Krabbe disease is 1:100,000 live births. It is believed that 80-90% of affected children will have the early infantile form of the disease (Wenger, 2001). Other forms of the disease, however, occur throughout life. Unfortunately, neither the level of enzyme activity nor identification of specific genetic mutation(s) reliably predicts phenotype. Since the only treatment for Krabbe disease is bone marrow transplantation, it is crucial to be able to identify prognostic factors, which will predict disease course.

At this time the literature is limited regarding the clinical signs and symptoms, age of onset, and survival of children with the later-onset forms of Krabbe disease. With the advent of universal newborn screening, the need to prospectively determine which child will develop the early infantile form (which requires emergent bone marrow transplantation), as opposed to more indolent later-onset forms, becomes of increasing importance. Although there is literature on the results of neurodiagnostic studies, it is limited. It is important to determine in a population of children who have been diagnosed with varying forms of the disease, which, if any, of these neurodiagnostic tests is predictive of disease course.

Determining the long-term developmental and functional outcomes of children with inherited metabolic diseases who have been identified by newborn screening should be an essential component of all newborn screening programs. Unfortunately, in New York State and elsewhere, long-term outcomes are not being assessed due to the high cost of neurologic and medical follow-up, and the barriers that prevent sharing of privileged medical information.

The New York State program of newborn screening for Krabbe disease is unique in that there is a statewide consortium of child neurologists who are committed to evaluating and following all children with positive newborn Krabbe disease screens ("the NYS Krabbe Consortium"). Dr. Patricia K. Duffner established the NYS Krabbe Consortium and the Krabbe World Wide Registry during her tenure as Clinical Director of the Hunter James Kelly Research Institute. The Krabbe Consortium began in 2006 when New York became the first state to screen for Krabbe disease. Children with positive newborn Krabbe disease screen are evauated and followed by using a specific schedule of agreed-upon neurodiagnostic and neurologic tests.

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Meet the Principal Investigators

Thomas J. Langan, M.D.

Thomas J. Langan, M.D. joined the Hunter James Kelly Research Institute (HJKRI) as Clinical Director in 2012, taking over for Dr. Patricia Duffner. Dr. Langan is a neurologist, specializing in Pediatrics, practicing at Women and Children's Hospital in Buffalo, NY. He leads LDN Pilot Project 4 (see page 4). Additionally, he serves as Associate Professor of Neurology, Pediatrics, and Physiology & Biophysics at the University at Buffalo.

Thomas J. Langan, M.D.

Dr. Langan's research background was focused originally on using astrocyte cell cultures to shed light upon processes related to astrogliosis and other responses of both developing and mature brain to injury. His research laboratory succeeded in modeling many of the immunochemical features of gliosis in primary brain cell culture. More recently, he has been involved in the clinical care of children with headache, demyelinating diseases, concussions, autism, and leukodystrophies in his role as Clinical Director of the Hunter James Kelly Research Institute, President of the New York State Krabbe Consortium, Director of the Headache and Concussion clinics at Children's Hospital of Buffalo, and as the Co-Director of the Pediatric MS clinic at Children's Hospital of Buffalo. His clinical leadership role in western New York can facilitate significant patient recruitment into multi-center research studies, an important aspect of successful research in the rare diseases.

In addition to presenting educational lectures to professional colleagues, Dr. Langan enjoys presenting community lectures about head injuries and other forms of brain injury. He has presented to groups of sports coaches and teachers about preventing brain injury in children. He has repeatedly been a talk-show radio guest in his region, educating listeners about children's learning disabilities, autism, and the prevention of concussion and other brain injury in children.

Selected Thomas J. Langan, M.D. Publications:

C.T. Turgeon, J.J. Orsini, K.A. Sanders, M.J. Magera, T.J. Langan, M.L. Escolar, P. Duffner, D. Oglesbee, D. Gavrilov, S. Tortorelli, P. Rinaldo, K. Raymond, D. Matern, Measurement of psychosine in dried blood spots – a possible improvement to newborn screening programs for Krabbe disease. J Inherit Metab Dis (2015) Published online 3-12-2015.

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Join the RDCRN Contact Registry

The Rare Diseases Clinical Research Network (RDCRN) **Contact Registry** exists to inform patients and/or parents of patients about clinical research studies. Joining the contact registry will help researchers identify and recruit patients who are eligible for participation in future research studies. This is critically important in rare disease research, because it is often very difficult for researchers to find enough patients who have any given rare disease, in order to reach statistical significance in their data analysis. If the level of statistical

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Check Your Knowledge of Lysosomal Diseases

How well do you know metachromatic leukodystrophy?

By Evelyn S. Redtree, M.S.

Introduction to an Understanding of Metachromatic Leukodystrophy

In the May 2014 issue of "**Indications**," *Check Your Knowledge of Lysosomal Diseases* presented information about Krabbe disease, one of the leukodystrophies. In this issue we will learn about another of the leukodystrophies: metachromatic leukodystrophy. (To access all past issues of "**Indications**" please see the links in the upper-right area of the LDN homepage at: www.LysosomalDiseaseNetwork.org.)

Metachromatic leukodystrophy ("MLD"), also known as cerebroside sulphatase deficiency disease; *ARSA* deficiency; arylsulfatase A deficiency disease; metachromatic leukoencephalopathy; sulfatide lipidosis; and sulfatidosis (among other names), is an autosomal recessive inherited disorder characterized by the accumulation of sulfatides, specifically cerebroside sulfate, inside lysosomes. Sulfatides are a class of sulfated galactosylceramides (sphingolipids) synthesized primarily in the oligodendrocytes in the central nervous system. They are thought to play a major role in myelin function and stability. Genetic mutations can result in a decreased ability to break down sulfatides inside the lysosome, resulting in their accumulation. Sulfatides especially accumulate inside the lysosomes and also in the plasma membrane of myelin.[1] Excess sulfatides are toxic to the nervous system. Sulfatide accumulation inside myelin-producing cells causes progressive destruction of white matter (leukodystrophy) throughout the nervous system, including the central nervous system and the peripheral motor and sensory nerves. While neurological problems are the primary feature of metachromatic leukodystrophy, effects of sulfatide accumulation on other organs and tissues have also been reported, most often involving the gallbladder, liver and kidneys.

Metachromatic leukodystrophy gets its name from the way cells with an accumulation of sulfatides appear under microscopy. The sulfatides form granules that are described as metachromatic, which means they pick up color differently than surrounding cellular material when stained for examination, or when exposed to polarized light.

Genetic Bases of MLD

Most individuals with metachromatic leukodystrophy have mutations in the *ARSA* gene (cytogenetic location 22q13.33), which provides instructions for making the lysosomal enzyme arylsulfatase A. More than 80 pathogenic mutations of the *ARSA* gene have been identified so far.[1] A small percentage of individuals with metachromatic leukodystrophy have mutations in the *PSAP* gene (cytogenetic location 10q22.1). This gene provides instructions for making a protein that is cleaved into smaller proteins that assist enzymes in breaking down various fats. One of these smaller proteins is called saposin B; this protein works with arylsulfatase A to break down sulfatides. Thus, this variant of MLD is called "metachromatic leukodystrophy due to saposin B deficiency."

In a small percentage of cases, individuals with very low levels of arylsulfatase A activity show no symptoms of metachromatic leukodystrophy. This condition is called "pseudoarylsulfatase deficiency."[1,5]

There are Three Main Classifications of Metachromatic Leukodystrophy

The most common form of metachromatic leukodystrophy, affecting about 50 to 60 percent of all individuals with this disorder, is called the **late infantile form**. Symptom onset usually occurs during the second year of life, or before 30 months of age. Affected children develop dysarthria, eventually losing any speech they have developed; they become weak; exhibit clumsiness, frequent falls and toe-walking with gait disturbance. As the disorder progresses, muscle tone first decreases, then increases to the point of rigidity. The individual experiences pain in the arms and legs; progressive deterioration of mental function; possible generalized or partial seizures; deterioration of vision and hearing, including optic atrophy; incontinence; and peripheral neuropathy. In the final stages, individ-

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uals exhibit tonic spasms and decerebrate posturing with unawareness of their surroundings. Individuals with the late infantile form of metachromatic leukodystrophy typically do not survive past childhood; death occurs within 5 years of symptom onset in most of these patients.

For 20 to 30 percent of individuals with metachromatic leukodystrophy, onset occurs between the age of 4 and adolescence/puberty. In this **juvenile form**, the first signs of the disorder may be behavioral problems and increasing difficulty with schoolwork. As the disease progresses, individuals exhibit progressive gait disturbance, dysarthria, clumsiness, possible seizures, spasticity, ataxia, optic atrophy and bizarre behaviors. The disease continues to progress, with the same final-stage signs and symptoms as the late infantile form. Progression of the disorder is slower than in the late infantile form, and affected individuals may survive for about 20 years after symptom onset.

The **adult form** of metachromatic leukodystrophy affects approximately 15 to 20 percent of individuals who have the disorder. In this form, the first symptoms appear after puberty, during the teenage years, or later—sometimes not until the fourth or fifth decade of life. In mild cases the diagnosis may even go unsuspected during life. The first symptoms to appear are often (but not always) behavioral problems such as alcoholism, drug abuse, or performance difficulties at school or work. The affected individual may experience personality changes, poor money management skills, labile emotions, and/or psychiatric symptoms such as delusions, paranoia, dementia or auditory hallucinations. A diagnosis of schizophrenia may initially be made. Disorders of movement and posture may appear late. In other cases, the initial signs and symptoms are neurologic (weakness and loss of coordination, progressing to spasticity and incontinence) or seizures. Peripheral neuropathy is common. People with the adult form of metachromatic leukodystrophy may survive for 20 to 30 years after symptom onset. During this time there may be some periods of relative stability, and other periods of more rapid decline. The final stage is similar to that for the earlier-onset forms.

Incidence of Metachromatic Leukodystrophy

The incidence of metachromatic leukodystrophy in the United States is estimated at 1:40,000. The global incidence of metachromatic leukodystrophy is estimated at 1:160,000. Due to widespread misdiagnosis, the true incidence is likely to be different. Due to founder effects, the condition is more common in certain genetically isolated populations: incidence is 1:75 in a small group of Jews who immigrated to Israel from southern Arabia (Habbanites); 1:2,500 in the western portion of the Navajo Nation; and 1:8,000 among Arab groups in Israel. In the United States, the mutation-carrier frequency averages 1:100. There is a 1:10,000 chance of two U.S. carriers becoming a couple.

How is Diagnosis Made?

Austin et al. (1964) were the first to determine that the causative defect concerns the lysosomal enzyme arylsulfatase A.[2] Austin's test to demonstrate absence of arylsulfatase A activity in the urine was a useful early diagnosis method (Greene et al., 1967).[3] Kaback and Howell (1970) demonstrated profound deficiency of arylsulfatase A in cultured skin fibroblasts of patients, and an intermediate arylsulfatase A deficiency in carriers.[4] In fact, assay of arylsulfatase A enzymatic activity cannot distinguish between metachromatic leukodystrophy and pseudoarylsulfatase deficiency.[5] In pseudoarylsulfatase deficiency, arylsulfatase A enzyme activity ranges from 5% to 20% of normal controls, yet this does not cause metachromatic leukodystrophy.[5] Further, for purposes of prenatal diagnosis, arylsulfatase A levels usually are low in mid-trimester amniotic cells; hence, homozygotes cannot be reliably identified by amniocentesis.[5] These obstacles mean that suspected MLD diagnosis must be confirmed by one or more of these additional tests: molecular genetic testing of *ARSA* (the only gene in which mutations are

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known to cause arylsulfatase A deficiency); the finding of metachromatic lipid deposits in nervous system tissue; or urinary excretion of sulfatides.[5] Carrier genetic testing of at-risk family members, and prenatal diagnosis for at-risk pregnancies, can be done if both disease-causing *ARSA* mutations have already been identified in an affected family member.[5]

Treatment of Metachromatic Leukodystrophy

Hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT) are being done, with encouraging results in only a limited subset of patients (Bayever et al. 1985; Krivit et al. 1990, de Hosson et al. 2011).[6,7,8] The best outcomes are obtained when HSCT or BMT is performed in the pre-symptomatic stage.[5] These procedures remain a difficult parental decision because of their substantial risk of death, and their uncertain long-term effects.[5] In a review of outcomes of persons with MLD undergoing HCST, Orchard and Tolar (2010) concluded that persons with later-onset MLD may benefit; and pre-symptomatic children with mutations typical for late-infantile onset appeared to have significant cognitive benefits; however, it remained unclear if progressive motor problems would improve.[5,9]

Umbilical cord blood transplantation in some post-symptomatic affected children has shown that cord blood transplant can improve *some* disease manifestations; and in some pre-symptomatic homozygous children, cord blood transplant can stop disease progression in MLD (Pierson et al. 2008).[5,10]

More recently, lentiviral transduced hematopoietic stem cell gene therapy was performed on three pre-symptomatic children with arylsulfatase A deficiency who were known because of their older siblings' early-onset MLD, and who were carrying the same mutations (Biffi et al. 2013).[11] After re-infusion of the gene-corrected hematopoietic stem cells, the patients showed extensive and stable *ARSA* gene replacement, which led to high arylsulfatase A expression throughout hematopoietic cell lineages and in the children's cerebrospinal fluid.[11] None of the first three patients that have been reported had progression of MLD at up to 24 months after treatment, even after the time of onset projected from their siblings' cases.[11]

It has been shown that providing a stimulating, enriched environment and an indefatigable physical therapy program results in improved quality of life at every disease stage of MLD patients.[5] Maintenance of patients' intellectual abilities, neuromuscular function, and mobility should be pursued as long as possible using proactive symptomatic interventions.[5] Caregivers should be educated about the likely progression of the disorder so that they can anticipate decisions concerning car seats, walking aids, wheelchairs, swallowing support, suctioning equipment, nutritional strategies and procedures, patient lifts, and other supportive interventions.[5] Seizures, contractures, gastroesophageal reflux, constipation, and drooling should be treated with appropriate pharmaceutical agents.[5] For children, a family physician should be a team member in developing comprehensive care plans that include all the usual pediatric vaccinations and other routine pediatric care.[5] To minimize catastrophic impacts upon the whole family, disease management should include a team of professionals to provide genetic counseling and family support throughout the protracted disease process.[5] Provision of a network of family support services is essential, as well as establishing contact with other families who have faced similar situations.[5] As in other lysosomal diseases, caring for MLD patients is clearly a team effort involving the community, the patient's family, and an extensive team of professionals in medical, palliative and social care.[5]

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Online Mendelian Inheritance in Man® - **Metachromatic Leukodystrophy due to Saposin B Deficiency**: http://www.omim.org/entry/249900?search=metachromatic%20leukodystrophy&highlight=leukodystrophy%20metachromatic

Gene Reviews® - **Arylsulfatase A Deficiency** http://www.ncbi.nlm.nih.gov/books/NBK1130/

NINDS Metachromatic Leukodystrophy Information Page: http://www.ninds.nih.gov/disorders/metachromatic_leukodystrophy/metachromatic_leukodystrophy.htm

Useful, thoughtfully-written "**Guide to MLD**" is a free download from The Society for Mucopolysaccharide Diseases (the MPS Society), in the U.K.: http://www.mpssociety.org.uk/conditions/related-diseases/metachromatic-leukodystrophy/

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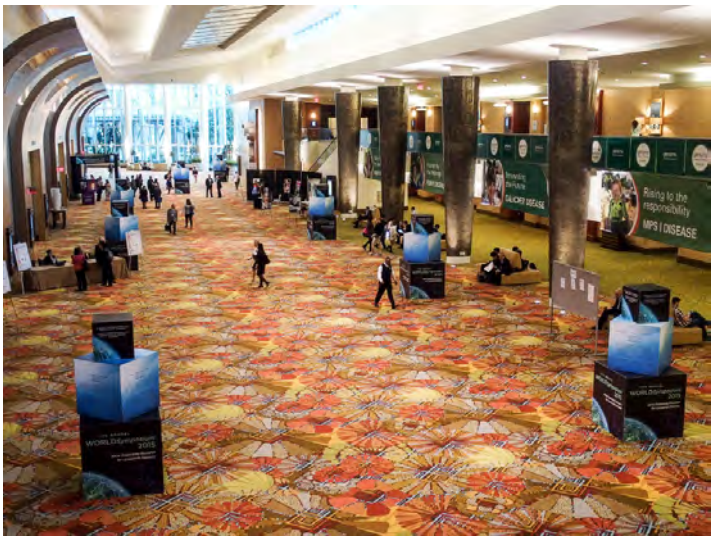
WORLD*Symposium* 2015 Views



Hyatt Regency Orlando was the setting for WORLD*Symposium* 2015.

Multiple poster sessions were a focus of intense education for attendees.

Chester B. Whitley PhD, MD (left) presents the 2015 Award for Innovation and Accomplishment in the field of lysosomal disease research and therapy to Stephen C. Groft, PharmD. For a brief yet astounding description of what Dr. Groft has done for the rare diseases community, read pages S3-S4 of *Molecular Genetics and Metabolism*, 114(2) (2015) . If not for him, the Lysosomal Disease Network would not exist.

Stephen C. Groft, PharmD presented the keynote address at WORLD*Symposium* 2015.

Hot Off the Press

Selected Recent Publications by Lysosomal Disease Network Investigators

L.D. Pena, A.D. Proia, P.S. Kishnani, Postmortem findings and clinical correlates in individuals with infantile-onset Pompe disease. JIMD Rep Mar 13 (2015) [Epub ahead of print]. PMID: 25763511. [PubMedCentral - in process].

K. L. Berrier, Z.B. Kazi, S.N. Prater, D.S. Bali, J. Goldstein, M.C. Stefanescu, C.W. Rehder, E.G. Botha, C. Ellaway, K. Bhattacharya, A. Tylki-Szymanska, N. Karabul, A.S. Rosenburg, P.S. Kishnani, CRIM-negative infantile Pompe disease: characterization of immune responses in patients treated with ERT monotherapy. Genet Med Mar 5 (2015) [Epub ahead of print]. PMID: 25741864. [PubMedCentral - in process].

Y.H. Chien, J.L. Goldstein, W.L. Hwu, P.B. Smith, N.C. Lee, S.C. Chiang, A.A. Tolun, H. Zhang, A.E. Vaisnins, D.S. Millington, P.S. Kishnani, S.P. Young, Baseline urinary glucose tetrasaccharide concentrations in patients with infantile- and late-onset Pompe disease identified by newborn screening. JIMD Rep Feb 15 (2015) [Epub ahead of print]. PMID: 25681082. [PubMedCentral - in process].

M. Mauer, E. Glynn, E. Svarstad, C. Tondel, M.C. Gubler, M. West, A. Sokolovskiy, C.B. Whitley, B. Najafian, Mosaicism of podocyte involvement is related to podocyte injury in females with Fabry disease. PLoS One 9(11) (2014) e112188. PMCID: PMC4227696. Article is freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4227696/

Related, Non-LDN-Funded Publications:

E.G. Shapiro, I. Nestrasil, A. Ahmed, A. Wey, K.R. Rudser, K.A. Delaney, R.K. Rumsey, P.A. Haslett, C.B. Whitley, M. Potegal, Quantifying behaviors of children with Sanfilippo syndrome: the Sanfilippo behavior rating scale. Mol Genet Metab Mar 5 (2015) pii: S1096-7192(15)00063-3 [Epub ahead of print]. PMID: 25770355. [PubMedCentral - in process].

S. Kansagra, S. Austin, S. DeArmey, Z. Kazi, R.M. Kravitz, P.S. Kishnani, Longitudinal polysomnographic findings in infantile Pompe disease. Am J Med Genet A Feb 23 (2015) [Epub ahead of print]. PMID: 25706820. [PubMedCentral - in process].

Q.K. Tan, D.W. Stockton, E. Pivnick, A.F. Choudhri, S. Hines-Dowell, L.D. Pena, M.A. Deimling, M.S. Freemark, P.S. Kishnani, Premature pubarche in children with Pompe disease. J Pediatr Feb 13 (2015) pii: S0022-3476(14)01262-1 [Epub ahead of print]. PMID: 25687635. [PubMedCentral - in process].

L.E. Case, C. Bjartmar, C. Morgan, R. Casey, J. Charrow, J.P. Clancy, M. Dasouki, S. DeArmey, K. Nedd, M. Nevins, H. Peters, D. Phillips, Z. Spigelman, C. Tifft, P.S. Kishnani, Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease. Neuromuscul Disord Dec 19 (2014) pii: S0960-8966(14)00724-X [Epub ahead of print]. PMID: 25617983. [PubMedCentral - in process].

V. Valayannopoulos, V. Malinova, T. Honzik, M. Balwani, C. Breen, P.B. Deegan, G.M. Enns, S.A. Jones, J.P. Kane, E.O. Stock, R. Tripuraneni, S. Eckert, E. Schneider, G. Hamilton, M.S. Middleton, C. Sirlin, B. Kessler, C. Bourdon, S.A. Boyadjiev, R. Sharma, C. Twelves, C.B. Whitley, Quinn A.G., Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. J Hepatol 61(5) (2014) 1135-1142. PMCID: PMC4203712.

R.K. Rumsey, K.R. Rudser, K.A. 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. PMCID: PMC4041612.

K.A. Delaney, K.R. Rudser, B.D. Yund, C.B. Whitley, P.A. Haslett, E.G. Shapiro, Methods of neurodevelopmental assessment in children with neurodegenerative disease: Sanfilippo syndrome. JIMD Rep 13 (2014) 129-137. PMCID: PMC4110329. Article is freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110329/

The LDN Awards the 2015 LDN Fellowship

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to identify disease-modifier gene(s) for this disease. Dr. Mori will publish at least one peer-reviewed article as a result of the LDN Fellowship project, and will present this research at a relevant scientific meeting.

The **2016** LDN Fellowship begins on September 1, 2015. The NIH mandates that research funded by the LDN Fellowship be "clinical research" directly involving lysosomal disease patients, or patient specimens. Soon the LDN will be contacting its e-mail list with an announcement requesting applications for the 2016 LDN Fellowship. Not on the LDN e-mail list? Go to the LDN home page and click on the green "Sign Up for the LDN Network" button in the upper-left area of the page at: www.LysosomalDiseaseNetwork.org.

LDN Research *Matters*

Pilot Project 4: Long Term Follow Up for Krabbe Disease

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Since newborn screening for Krabbe disease is relatively new, it is unknown whether children with very low levels of galactocerebrosidase (the missing enzyme in this disorder) will have learning or other developmental disorders, or if the onset of the disease will occur later in life. Key to this study is to determine whether children with very low galactocerebrosidase enzyme activity, but no clinical evidence of Krabbe disease, are at risk for developmental and functional delays.

This project's data-gathering technique may serve as a surrogate tool in place of more costly comprehensive neuropsychological testing. Under the Pilot Project 4 protocol, all children with positive Krabbe disease newborn screens identified in New York State (or diagnosed by other means) (estimated at approximately 30-35 patients) will be followed for 5 years. These will include all New York State children who are asymptomatic or pre-symptomatic and who are currently enrolled in the Krabbe World Wide Registry, as well as any newly-diagnosed children during the 5-year period.

A Hunter's Hope Foundation staff member will conduct phone interviews at 4, 8, 12, 18, 24 months, and every 6 months for 5 years. The testing materials used in this phone-based data collection include both developmental and functional assessments. Results of the developmental/functional assessments will be sent to the referring neurologist. Children considered at risk for developmental delays will be referred to a New York State Early Intervention Program in their geographic area. The de-identified data from the phone interviews will be entered into the outcomes section of the Krabbe World Wide Registry, and into the LDN's database at the Data Management and Coordinating Center. If this Pilot Project is successful, the intention is to expand this program to other groups of children who have been identified on newborn screening as inheritors of metabolic disease.

References Cited:

M.E. Msall, Developing preschool surveillance tools for adaptive functioning: lessons for neuro-oncology. Eur J Paediatr Neurol 14(5) (2010) 368-379. PMID: 2047-1877.

D.A. Wenger, K. Suzuki, Y. Suzuki, Galactosylceramide lipidosis: globoid cell leukodystrophy (Krabbe disease). In: C.R. Scriver, A.L. Beaudet, D. Valle, W.S. Sly, eds. *The metabolic and molecular bases of inherited diseases*. 8th edition. New York: McGraw-Hill (2001) 3669-3694.

Join the RDCRN Contact Registry

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significance cannot be attained due to lack of sufficient numbers of subjects, then researchers assume that any beneficial results they recorded during their study could have been due to chance, not to their study's intervention(s).

Patients who participate in research make it possible for researchers to find new treatments, create new

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FDA to Hold Public 2-Day Workshop

Public Workshop on Assessment of Neurocognitive Outcomes in Inborn Errors of Metabolism and Advancing the Development of Pediatric Therapeutics: Assessment of Neurocognitive Outcomes

The FDA's Division of Gastroenterology and Inborn Errors Products, and Division of Pediatric and Maternal Health, both part of the Center for Drug Evaluation and Research (CDER), and the Office of Pediatric Therapeutics in the Office of the Commissioner, are announcing a **free** 2-day public workshop, "Assessment of Neurocognitive Outcomes in the Inborn Errors of Metabolism" and "Advancing the Development of Pediatric Therapeutics: Assessment of Pediatric Neurocognitive Outcomes." There is no fee to attend the public workshop, but attendees must register in advance. Space is limited, and registration for in-person attendance will be on a first-come, first-served basis.

Day 1 of the workshop will focus on approaches for assessing the efficacy of therapeutic products based on neurocognitive outcomes in patients diagnosed with inborn errors of metabolism disorders. The session will address the role of natural history studies and methodological approaches for selecting appropriate assessment scales and standardizing neurocognitive assessments. On Day 2 of the workshop, participants will discuss identification of signals in animal studies and clinical trials that warrant further clinical investigation and testing that may be predictive of neurocognitive outcome in children. Participants will also discuss strategies and methods to address the challenges of assessing long-term neurocognitive outcomes for products used to treat pediatric patients.

When: April 16 and 17, 2015, 8:00 a.m. to 5:00 p.m.

Where: FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, the Great Room (Rm. 1503A), Silver Spring, MD 20993-0002. Entrance for the public workshop participants (non-FDA employees) is through Bldg. 1, where routine security check procedures will be performed.

Participation can be either in-person attendance or by **webcast**. Persons interested in attending this workshop must register by sending an email to: Neurocognitive_workshop@fda.hhs.gov **before March 31, 2015**. More details regarding registration are at: http://www.fda.gov/Drugs/NewsEvents/ucm434954.htm.

National Center for Advancing Translational Sciences (NCATS) releases Notice of Intent to Publish Funding Opportunity Announcements

During February 2015, the National Center for Advancing Translational Sciences (NCATS) released Notices of Intent to Publish Funding Opportunity Announcements. The notice numbers are: NOT-TR-15-005 and NOT-TR-15-006. They can be found online at: http://grants.nih.gov/grants/guide/notice-files/NOT-TR-15-005.html *and* http://grants.nih.gov/grants/guide/notice-files/NOT-TR-15-006.html.

These funding opportunity announcements (FOA) will utilize the X02 pre-application activity code, with pre-applications due in May 2015; and the U01 Research Project–Cooperative Agreement, with applications due winter 2015. The Notices of Intent to Publish were provided to allow potential applicants sufficient time to develop meaningful collaborations and responsive projects for the U01 application. Since the U01 is an application, rather than pre-application, letters of Institutional commitment, detailed budget information, and information about the protection of human subjects will be required, if applicable for the proposed collaborative projects.

The U01 FOAs will invite applications for innovative collaborative investigations (involving three or more CTSA sites) into improvements of the methods of translational research; and addressing high priority translational research questions. Among other requirements, such projects should develop a new technology, method, or approach that addresses a general roadblock in science and/or operations that limits the efficiency and effectiveness of translation. These FOAs also will support innovative approaches to training or community/patient engagement that are focused on improving translation. Proposed projects should also advance collaboration, building on existing strengths and resources of CTSA hubs.

Calendar of Upcoming Events

2015 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, March 24 - 28, 2015 at the Salt Palace Convention Center, and the Salt Lake Marriott Downtown at City Creek, and the Hilton Salt Lake Downtown Hotel in Salt Lake City, Utah. Exhibit dates: March 25 - 27, 2015. Visit: http://ww4.aievolution.com/acm1501/

Cystinosis Research Foundation's Sixth Annual Day of Hope Cystinosis Family Conference, April 16 - 18, 2015 at Balboa Bay Resort, 1221 West Coast Highway, Newport Beach, CA 92663. Call Gina for reservations at (949) 630-4211. Visit: http://www.cystinosisresearch.org/day-hope-2015-crf-family-conference/

National Tay-Sachs and Allied Diseases 37th Annual Family Conference, April 16 - 19, 2015 at Hyatt Regency Reston, 1800 Presidents Street, Reston, Virginia. Visit: http://www.ntsad.org/index.php/event-listings/family-conference/2015-conference

American Society of Gene & Cell Therapy 18th Annual Meeting, May 13 - 16, 2015, in New Orleans, Louisiana. Visit the ASGCT homepage: http://www.asgct.org/

The Calliope Joy Foundation's *An Evening with Jim & Jill Kelly for Hunter's Hope* to benefit a National Care Network for Leukodystrophies, Friday, May 15, 2015 at the Rittenhouse Hotel, Philadelphia, Pennsylvania. VIP Reception starts 6:00 p.m.; Dinner 7:00 - 10:00 p.m. Event Chair, Maria Kefalas: mkefalas67@gmail.com. Visit: http://www.thecalliopejoyfoundation.org/ Sold Out

Every Step Walk for Hunter's Hope Foundation, Saturday, May 16, 2015, in Fairmount Park, Philadelphia, Pennsylvania, beginning at 4231 Avenue of the Republic, Memorial Hall. This is a 3-mile family-fun walk–handicap and stroller friendly. Registration opens 8:00 a.m. and the walk begins at 8:30 a.m. Funds raised will support establishment of the Leukodystrophy Care Network's Leukodystrophy Care Center ("LCC") at Children's Hospital of Philadelphia. For details, visit: http://www.hopehope.org/site/TR/EveryStep Walk/General?fr_id=1821&pg=entry

The annual "Michael, Marcia & Christa Parseghian Scientific Conference" for Niemann-Pick type C disease research will be held June 11 -13, 2015 at the University of Notre Dame. Researchers will gather for three days to discuss the advances in NP-C research. This yearly meeting helps to form collaborations and determine the future direction of NP-C research. Visit: http://www.parseghian.org/events.html or call: (520) 577-5106.

Canadian Association of Pompe's 2015 "CAP Conference and AGM" will be held in Montreal, Quebec, Canada, June 20 - 21, 2015. For further information, visit: http://www.pompecanada.com/events/109-2015-cap-conference-and-agm-save-the-date

Batten Disease Support and Research Association Family Conference 2015, July 9 - 12, 2015 at The Eaglewood Resort and Spa, 1401 Nordic Road, Itasca, Illinois, USA. Visit: http://bdsra.org/ and www.eaglewoodresort.com

United Leukodystrophy Foundation's 2015 Annual Scientific Meeting and Family Conference, July 15 - 18, 2015 at Embassy Suites Downtown Old Market in Omaha, Nebraska, USA. Visit: http://ulf.org/conferences

Cystinosis Research Network 2015 Family Conference, July 16 - 18, 2015 at Doubletree by Hilton Chicago Magnificent Mile, Chicago, IL, USA. Visit: https://cystinosis.org/news/announcements/188-2015-family-conference-announced

Glycoproteinoses: Fourth International Conference on Advances in Pathogenesis and Therapy (a combined scientific and family conference), July 23 - 26th, 2015, in St. Louis, Missouri, USA. Visit: www.ISMRD.org

The Association for Glycogen Storage Disease 2015 Family/Professional Conference, September 18 - 19, 2015 in Oklahoma City, OK. For updates, visit: http://www.agsdus .org/

Join the RDCRN Contact Registry

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studies, and work for the improvement of quality of life of those affected by rare diseases. Those who have joined the RDCRN Contact Registry are available to be contacted in the future about clinical research opportunities and updates on the progress of the research projects. The RDCRN contact registry is anonymous and free of charge.

After you have joined and submitted information online, the data is stored in a secure database. No personal identifying information (such as your name, address, telephone number) will be given to *anyone* without your expressed approval. For details: http://www.rarediseasesnetwork.org/registry/index.htm

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

Keys to Understanding the Lysosomal Disease Network

Lysosomal Disease Network