Indications™

Newsletter of The Lysosomal Disease Network™

April 2014 Vol. 1, No. 5

Keys to Understanding the Lysosomal Disease Network

Who has benefited from the Training/ Educational Core's Fellowships? What research resulted from these Fellowships?

By Evelyn S. Redtree, M.S.

As detailed in the March 2014 issue of '**Indications**,' two post-doctoral Lysosomal Disease Network Fellows are recruited each year. One Fellowship is funded through LDN NIH funds. The University of Minnesota Medical School provides $50,000 matching funds for an additional post-doctoral Fellow, who is located at the University of Minnesota in the Twin Cities. Fellows are selected by the LDN Steering Committee, and can elect training in any clinically-related field such as clinical genetics, neurology, neuropsychology, or any field of medicine that might provide research or clinical service for patients with lysosomal disease. The LDN Fellows spend half of their time in one center, devote some time to clinical research, and travel to other laboratories or clinical services to broaden their experience. They are required to present their research at the LDN's WORLD*Symposium*™, and at the biennial Conference on Clinical Research for Rare Diseases (CCRRD) presented by the Rare Diseases Clinical Research Network.

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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 . . .

National MPS Society

http://mpssociety.org/
https://www.facebook.com/pages/National-MPS-Society/35203705783?ref=hl
https://twitter.com/MPSSociety

The mission statement of the National MPS Society states "The National MPS Society exists to find cures for MPS and related diseases. We provide hope and support for affected individuals and their families through research, advocacy, and awareness of these devastating diseases."

The National MPS Society was founded in February 1974 in a conference room at Johns Hopkins Hospital by a small group of parents of MPS-affected children. At that time, the goal was to learn more about these disorders, and to form mutually-supportive relationships within the parent group. They chose the name "Parents for MPS" for this group. The parents agreed

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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.

Who has benefited from the Training/ Educational Core's Fellowships? What research resulted from these Fellowships?

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Past LDN Fellows are listed below, along with their LDN mentor, and any available publication(s) or abstracts presenting their research findings:

Julie Eisengart, Ph.D. was mentored by Elsa Shapiro, Ph.D. at University of Minnesota.
J.B. Eisengart, K.D. Rudser, J. Tolar, P.J. Orchard, T. Kivisto, R.S. Ziegler, E.G. Shapiro, Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediat 162(2) (2013) 375-380. PMCID: PMC3524404.

Sarah Lo, M.D. was mentored by Pramod Mistry, M.D., Ph.D. at Yale University.
S.M. Lo, J. Liu, F. Chen, G.M. Pastores, J. Knowles, M. Boxer, P.K. Mistry, Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. J Inherit Metab Dis 34(3) (2011) 643-650. PMCID: PMC 378-2382.

Jeanine Utz, PharmD, was mentored by James C. Cloyd, PharmD at the University of Minnesota.
J.R. Utz, P. Sorgen, T. Crutcher, C.B. Whitley, Metabolomic study of CSF and serum markers in infantile and juvenile gangliosidosis diseases. Mol Genet Metab 111(2) (2014) S107.

Moin Vera, M.D., Ph.D. was mentored by Patricia I. Dickson, M.D. at Harbor-UCLA Medical Center.
M. Vera, S. Le, S.H. Kan, H. Garban, D. Naylor, A. Mlikotic, I. Kaitila, P. Harmatz, A. Chen, P. Dickson, Immune response to intrathecal enzyme replacement therapy in mucopolysaccharidosis I patients. Pediatr Res 74(6) (2013) 712-720. PMCID: PMC3855632.

Jonica Hazaert, PharmD was mentored by Jeanine Utz, PharmD and James Cloyd, PharmD at the University of Minnesota. Research still underway, being completed by a subsequent LDN Fellow.

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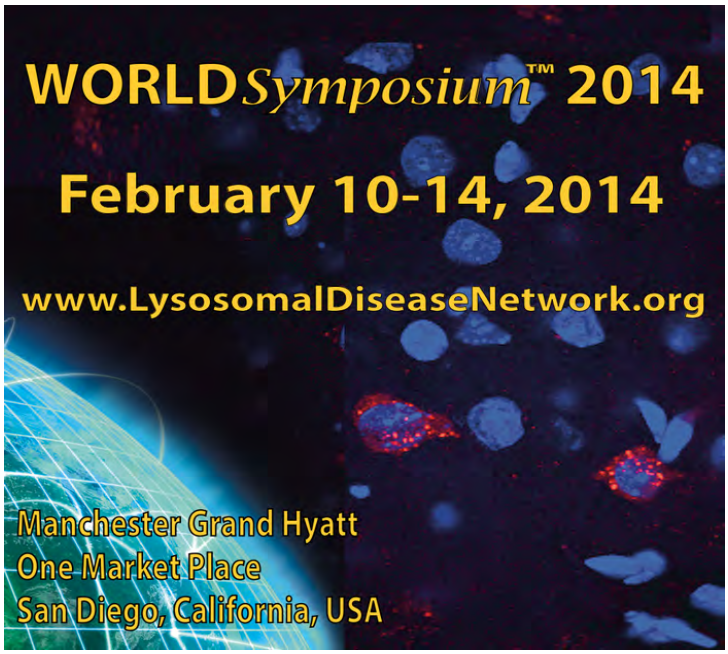

The 10th Annual WORLD*Symposium*™ Highlights in Review: Part II

The 10th annual WORLD*Symposium* 2014 presented platform presentations focused on translational science on Wednesday, February 12th. Following Dr. Richard Moscicki's presentation (covered in the March 2014 issue of '**Indications**'), 24 researchers presented their findings. These included Kathryn Sheets, Priya S. Kishnani and colleagues at Duke University Medical Center, who aimed to assess the natural history and treatment outcomes in a 46-case cohort of cross-reactive immunologic material (CRIM)-negative infantile Pompe disease patients to determine how often CRIM-negative patients mount an immune response against infused recombinant human GAA (rhGAA) replacement enzyme. This is of special interest partly because sporadic CRIM-negative cases lacking significant immune responses have emerged in recent literature. After excluding those with prophylactic immune tolerance induction treatment, the investigators completed retrospective analysis of outcome measures for 20 CRIM-negative infantile Pompe disease patients receiving ERT monotherapy with rhGAA.

All 20 patients developed anti-rhGAA antibodies, with 65% (13/20) mounting high sustained antibody titers (HSAT). Four patients maintained intermediate antbody titers, while three had low antibody titers.

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Who has benefited from the Training/ Educational Core's Fellowships? What research resulted from these Fellowships?

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Wenyong Tong, Ph.D. was mentored by Jeffrey Esko, Ph.D. at University California, San Diego.
W. Tong, S. Sarrazin, Y. Tor, J. Esko, Novel transporters for MPS I and MPS IIIA enzyme replacement therapy. Mol Genet Metab 108(2) (2013) S92.

Alia Ahmed, M.D. was mentored by Elsa Shapiro, Ph.D. at University of Minnesota.
A. Ahmed, C.B. Whitley, R. Cooksley, K. Rudser, S. Cagle, N. Ali, K. Delaney, B. Yund, E.G. Shapiro, Neurocognitive and neuropsychiatric phenotypes associated with the mutation L238Q of the α-L-iduronidase gene in Hurler-Scheie syndrome. Mol Genet Metab 111(2) (2014) 123-127. PMCID: PMC3939822.

Patrick Sorgen, PharmD is being mentored by Jeanine Utz, PharmD and James Cloyd, PharmD at the University of Minnesota.
Dr. Sorgen is completing research begun by Jonica Hazaert, PharmD. When completed, this research will be submitted for publication.

Kelly King, Ph.D. is being mentored by Elsa Shapiro, Ph.D. at University of Minnesota.
K. King, K. Rudser, V. Kovac, I. Nestrasil, K. Delaney, E.G. Shapiro, Visual perceptual functioning and associated brain volumetrics in individuals with MPS I and II. Mol Genet Metab 108 (2013) S54.

Announced at WORLD*Symposium* 2014, the 2014 LDN Fellow is Zoheb Kazi, MBBS, of Duke University. Dr. Kazi is a native of India, and has been at Duke University since July 2013. He aspires to complete his medical residency, then subsequently work in an academic setting in North America practicing medicine, teaching and performing research. Dr. Kazi is being mentored by Priya Kishnani, M.D. Dr. Kazi's research will use: 1) whole exome sequencing (WES); 2) human leukocyte antigen (HLA) typing; 3) comprehensive immune phenotyping; and 4) differential expressions proteomics in patients with Pompe disease who have demonstrated atypical/unexpected antibody responses, as well as those with typical/expected antibody responses to enzyme replacement treatment (ERT) with recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa). The purpose of his research is to predict, prior to the initiation of ERT, which patients are at risk for developing high antibody titers. An "omics" approach aims to identify modifier genes and proteomic signature profile, as well as gain a greater understanding of factors influencing immune response (HLA type and other immunologic factors) to identify the patients likely to mount an immune response to ERT. This information will help guide optimal implementation of immune tolerance inducing (ITI) agents, resulting in improved therapeutic outcomes and maximal long-term benefits for these patients.

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National Niemann-Pick Disease Foundation announces the 2014 Peter G. Pentchev & Edward H. Schuchman Research Fellowships

The NNPDF will fund research fellowships in all areas of promise–basic, translational and clinical– with regards to Niemann Pick disease. Specifically, they are requesting applications for research fellowships to improve the understanding of the biology and pathogenesis of Niemann-Pick disease type C (the Peter G. Pentchev Fellowship) and acid sphingomyelinase deficiency (ASMD), Niemann-Pick disease types A and B (the Edward H. Schuchman Fellowship).

Applicants must be currently associated with a recognized laboratory. Pre-doctoral students must have a lab selected and an approved thesis. Applications will be accepted from pre-doctoral, M.D., Ph.D and D.V.M postdoctoral researchers, and early career investigators. The fellowships provide support of $50,000 per annum for two years ($30,000 per annum for three years for pre-doctoral fellowships) and may be renewable based on performance.

Applications are due May 1, 2014. Applicants will be informed of the funding decision by September 1, 2014, via e-mail. Fellowships awarded will begin October 1, 2014.
Visit: http://www.nnpdf.org/npresearch_01.html

The 10th Annual WORLD*Symposium*™ Highlights in Review: Part II

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They believe that variable immune responses in this small subset of CRIM-negative infantile Pompe disease warrants further investigation into the influence of genotype, age at start of ERT, potential human leukocyte antigen involvement and other genomic factors. They concluded that their data provide further evidence that CRIM-negative infantile Pompe disease patients receiving ERT monotherapy develop HSAT, with reduced survival and poorer clinical outcomes regardless of initiation of ERT. As opposed to prolonged immune tolerance induction treatment in the entrenched setting, with its greater safety risks and reduced likelihood of success, CRIM-negative infantile Pompe disease necessitates prophylactic immune tolerance induction treatment to prevent HSAT. Their abstract is #224 in the *Molecular Genetics & Metabolism* February 2014 issue.

Frits A. Wijburg and colleagues of Academic Medical Center, Amsterdam, Netherlands sought a reliable way to identify mucopolysaccharidosis type I (MPS I) classic newborns that would differentiate classic Hurler syndrome (MPS IH) infants from MPS I attenuated infants. This is needed because the current standard-of-care for Hurler syndrome is hematopoietic stem cell transplantation (HSCT) very early in life, when it is most effective in preventing CNS damage. Dr. Wijburg's group developed and tested an algorithm predicting phenotypic severity in newborn MPS I patients. In the initial phase, 30 MPS I patients were included. Genotypes were collected from all patients, and all patients were phenotypically categorized at age 18 months based on the clinical course of the disease. Homozygosity or compound heterozygosity for specific mutations known to be associated with MPS IH were identified in order to discriminate a subset of patients with MPS IH from patients with more attenuated phenotypes (specificity 100%, sensitivity 88%). Then they found that improved enzymatic analysis of α-L-iduronidase (IDUA) activity in fibroblasts partially allows separation of Hurler from non-Hurler patients. Therefore, residual α-L-iduronidase activity in fibroblasts was introduced as the second step in the algorithm. Patients with intermediate IDUA activity could be further classified by the presence of differentiating clinical characteristics, resulting in a model with a predicted 100% sensitivity and specificity for this cohort of patients. Using genetic, biochemical and clinical characteristics, all potentially available during the newborn period, an algorithm was developed for reliable prediction of the MPS IH phenotype. This makes early decisions about the optimal treatment strategy feasible for MPS IH patients identified by newborn screening. Their abstract is #272 in the *Molecular Genetics & Metabolism* February 2014 issue.

Joseph V. Rutkowski and colleagues of Synageva BioPharma, BRM, Inc. and Covance, Inc. had previously reported initial findings from a mucopolysaccharidosis type IIIB mouse model showing that both intravenously (IV) and intrathecally (IT) administered recombinant form of human α-N-acetylglucosaminidase (NAGLU) enzyme (known as SBC-103) decreased brain heparan sulfate disaccharide with a concomitant increase in brain NAGLU enzyme activity. Building upon this work, NAGLU activity and heparan sulfate disaccharide (HSD) levels were measured in tissue from NAGLU (-/-) mice in separate studies following (i) IV administration once weekly for 3 to 6 weeks; (ii) IV administration once weekly for 4 weeks; and (iii) IT administration once every other week for 12 weeks. Each dosing cohort tested three different dose-strengths. Their results revealed dose-dependent reductions in heparan sulfate in NAGLU (-/-) mice with IV dosing of SBC-103. Reductions were also seen with IT dosing, but a minimally-effective dose was not defined across the three doses tested. Decreases in heparan sulfate were accompanied by increases in perfused brain α-N-acetylglucosaminidase enzyme activity levels. They concluded that their data confirmed their initial findings of the effects of IV administered SBC-103 on CNS substrate accumulation in this disease model, and supported further investigation of IV dosing of SBC-103 as an approach for patients with MPS IIIB. Their abstract is #210 in the *Molecular Genetics & Metabolism* February 2014 issue.

Dao Pan and colleagues of Cincinnati Children's Hospital Medical Center and the University of Cincinnati

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concerned themselves with the inability of enzyme replacement therapy for mucopolysaccharidosis type I to remediate CNS damage, due to the blood-brain barrier (BBB). They had recently identified a receptor-binding peptide (Rb) from apolipoprotein E that facilitated a widespread CNS delivery of α-L-iduronidase (IDUA)-Rb fusion protein (IDUAe) via transcytosis, mediated by low-density lipoprotein receptor-related protein 1 (LRP-1) (Wang D. et al. PNAS 2013). Building upon that work, using MPS I mice they evaluated the long-term brain biodistribution and therapeutic benefits in correlation with plasma IDUAe levels and transgene dosages after hematopoietic stem cells (HSCs)-mediated gene transfer with a lentiviral vector using an erythroid/megakaryocyte specific promoter. Based on plasma IDUA levels, MPS I animals treated with IDUAe or control IDUAc (IDUA fused with myc-tag) were divided into four dosage groups: low, medium, medium-high and high.

Results showed significantly higher IDUA activities (up to 10-fold) in IDUAe-treated mice than those in IDUAc-treated mice within same dosage groups. Metabolic glycosaminoglycan (GAG) accumulation in forebrain was significantly reduced in the IDUAe-medium and IDUAe-medium-high dosage groups, and was normalized in IDUAe-high dosage groups. In cerebellum where expression of LRP1 is relatively abundant, GAG levels were significantly reduced in the IDUAe-low dosage group, with normalization threshold at IDUAe-medium dosage. IDUAe protein was detected in neurons, astrocytes and microglia, with more intensive distribution around the brain ventricles and cerebellum Purkinje cells. Importantly, brain pathology was 50% reduced in IDUAe-medium dosage treatment group, an improvement that was better than those observed in IDUAc-high dosage group. Neurological memory impairment in MPS I mice was significantly improved in the IDUAe-medium and medium-high dosage groups, and was completely normalized in the IDUAe-high dosage groups. Overall, these findings not only demonstrate that long-term systemic delivery of BBB-targeted IDUAe could achieve superb neurological benefits for MPS I disease treatment, but also provide proof-of-concept evidence for the usage of Rb-tag as an effective strategy in treating neurological lysosomal-diseases and other CNS diseases. Their abstract is #186 in the *Molecular Genetics & Metabolism* February 2014 issue.

R. Scott McIvor and colleagues at the University of Minnesota, the Health Partners Research Foundation, and ReGenX Corporation had recently reported high levels of α-L-iduronidase (IDUA) in all parts of the brain of adult (10-month old) MPS I mice infused intracerebroventricularly at birth with adeno-associated virus (AAV) serotype 8 vector transducing the human IDUA gene (D.A.Wolf et al. Neurobiol Dis 43 (2011)123-133). Their experiments showed that direct, AAV-mediated IDUA gene transfer provides higher levels of enzyme in the MPS I brain than enzyme replacement therapy or hematopoietic stem cell transplant for prevention of storage accumulation and progression of CNS neurologic disease. Building upon this work, for initial clinical testing of AAV-mediated IDUA gene transfer to the CNS, they sought a less invasive route of vector administration that would be more acceptable than intracranial infusion for patients already undergoing enzyme replacement therapy and considering allogeneic hematopoietic stem cell transplant.

A CAGS-regulated AAV9 vector transducing the human IDUA gene was infused intrathecally or intranasally into MPS I mice. The mice were also treated with cyclophosphamide, to prevent anti-IDUA immune response, and with mannitol to promote vector diffusion into the brain. In the AAV9-IDUA intrathecally-injected mice, high levels of IDUA were found in all parts of the brain, with the highest levels observed in the hindbrain (cerebellum and brainstem) but levels that were nonetheless corrective in the midbrain (hippocampus, striatum) and cortex. Reduced levels of GAG storage were also found in the intrathecally-injected animals.

Surprisingly, corrective levels of IDUA activity were also found in all parts of the brain following intranasal infusion of AAV9-IDUA, with the highest level observed in the olfactory bulb. These results provide

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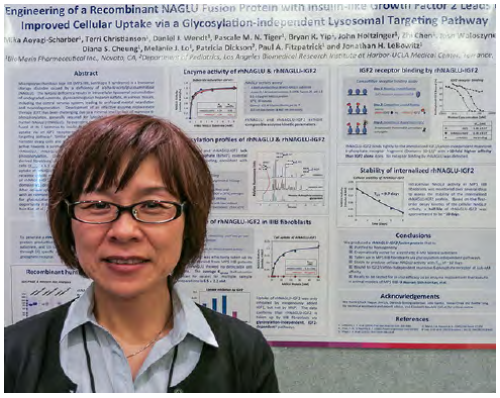
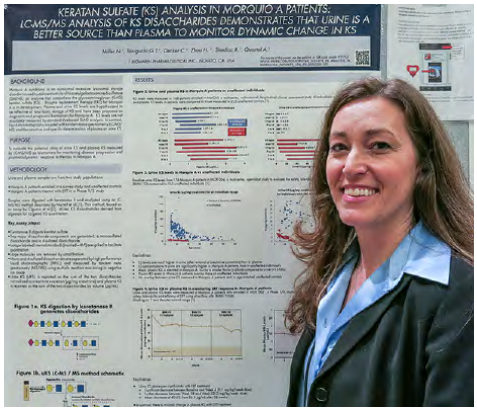
evidence for effective treatment of MPS I by direct, AAV9-mediated IDUA gene transfer to the brain using non-invasive routes of administration likely to be more acceptable to patients, families and physicians. Their abstract is #162 in the *Molecular Genetics & Metabolism* February 2014 issue.



Mika Aoyagi-Scharber, Ph.D. presented her poster of Abstract #14 at WORLD*Symposium* 2014.

Among the exciting posters exhibited was that of Mika Aoyagi-Scharber and colleagues of BioMarin Pharmaceutical Inc., and Patricia Dickson of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, presenting their abstract #14 entitled "Engineering of a recombinant NAGLU fusion protein with insulin-like growth factor 2 leads to improved cellular uptake via a glycosylation-independent lysosomal targeting pathway." They used MPS IIIB (Sanfilippo syndrome type B) patient-derived fibroblasts to test their engineered recombinant human NAGLU (rhNAGLU) fused at its C-terminus to insulin-like growth factor 2 (IGF2) to facilitate cell uptake via an IGF2 receptor-mediated, glycosylation-independent lysosomal targeting pathway. Similar to rhNAGLU, rhNAGLU-IGF2 is trimeric in solution, and active towards a synthetic 4-methylumbelliferyl substrate. As expected, like rhNAGLU, rhNAGLU-IGF2 contains a minimal level of mannose 6-phosphorylation. Consequently, in the uptake assay only rhNAGLU-IGF2, not rhNAGLU, was endocytosed into the cells under the experimental conditions; the observed uptake of rhNAGLU-IGF2 was mediated by the glycosylation-independent, IGF2-receptor specific mechanism. After cellular uptake, NAGLU activity remains detectable in the MPS IIIB fibroblasts with an estimated half-life of ~10 days. They concluded that rhNAGLU-IGF2 fusion protein engineered for glycosylation-independent lysosomal targeting offers a promising opportunity in developing highly effective ERT for MPS IIIB.

Another exciting poster was that of Nicole Miller and colleagues of BioMarin Pharmaceutical Inc., presenting their abstract #166 entitled "Keratan sulfate (KS) analysis in patients with Morquio syndrome type A: LC-MS/MS analysis of KS disaccharides demonstrates that urine is a better source than plasma to monitor dynamic change in KS." They found that urine is a better source than plasma to monitor dynamic changes in keratan sulfate as measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS). The reasons for their conclusion are: 1) urine has higher concentrations of keratan sulfate than plasma and excretion of keratan sulfate in urine is significantly higher in Morquio syndrome type A patients than in unaffected individuals; 2) plasma keratan sulfate is elevated in Morquio syndrome type A, but by a smaller factor (approximately 2-fold) compared to urine (approximately 15-fold); 3) plasma keratan sulfate concentrations in Morquio syndrome type A patients overlap those from unaffected persons; and 4) treatment of 18 Morquio syndrome type A patients with enzyme replacement therapy in a Phase I/II study resulted in a reduction of urine keratan sulfate (mean decrease 40.6% from 26.4 µg/mL after 36 weeks) and minimal change in plasma keratan sulfate (mean decrease 3.6% from 1.5 µg/mL after 36 weeks). This is a useful discovery in diagnosis and treatment assessment, since keratan sulfate levels are not accurately measured by standard dye-based GAG analysis.



Dr. Nicole Miller presented her poster of Abstract #166 at WORLD*Symposium* 2014.

The 10th Annual WORLD*Symposium* Highlights In Review will continue in the next issue of '**Indications**.'

LDNed@umn.edu

Meet Our Patient Advocacy Groups

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that the publication of a newsletter to share and provide information was a priority, and fundraising projects were subsequently undertaken. Additionally, the organization realized the need to expand existing research and to promote new research. At the June 1974 meeting, officers were elected to a temporary Board, and the name was changed to "The MPS Society." The Board created a "Parents Referral Plan" to connect MPS families with each other to discuss their mutual concerns and share emotional support. The Board began learning the complex medical information about these disorders in order to better inform the members of the organization.

September 1975 was a milestone for the MPS Society, with the organization becoming incorporated and holding the first seminar, attended by 33 people. By May 1976 the organization boasted a membership of 34 families. By 1979 the membership increased to 150, with a mailing list of 250. Fast-forward to 2014, and the National MPS Society has a mailing list of over 9,000 supporters and a membership of 700! These days, the Society's primary outreach tool is its outstandingly excellent Web site: http://mpssociety.org/. Its superb periodic newsletter, ***Courage***, is a benefit of membership.

Barbara Wedehase, MSW, CGC, has been the Executive Director of the National MPS Society since 2000. Her energized leadership of outstanding staff and volunteers is manifested in the wide range of ongoing activities of the Society. The activities of the National MPS Society encompass every possible layman's avenue to finding cures for MPS and related diseases, and for supporting the individuals and families affected by MPS. Their earliest enterprise, publishing, has grown into an extensive library of pamphlets and fact-sheets, many also available in Spanish, covering every relevant topic related to living with MPS, including but not limited to: explanations of each of the syndromes, disease management, education strategies and resources, possible complications of anesthesia, the emotional and physical sequelae of MPS and mucolipidosis II and III (ML II and III), and bereavement support. All of their publications are available as freely-downloadable .pdf documents. The scope and number of their fact-sheets is vast, and can be downloaded at: http://mpssociety.org/education/mps-fact-sheets/.

Barbara Wedehase, Executive Director of the National MPS Society (left), Kendra Gottsleben (center), and Kirsten Harkins, Executive Director of the Canadian MPS Society (right), at the 2013 National MPS Society's Annual National Family Conference in San Antonio, TX.

In 2006, the Society partnered with the Canadian MPS Society to publish an educational booklet entitled "Daily Living with MPS and Related Diseases." The National MPS Society is a member of the International MPS Network (www.impsn.org), the official global organization of MPS patient advocacy associations. The international MPS societies have reciprocity of written materials, and meet yearly to ensure that critical scientific and treatment information is shared both among and within countries, and with their patients.

The National MPS Society fundraising committee meets regularly to discuss funding opportunities and programs. It describes itself as a forward thinking committee that strives to research new ways of giving, and to raise both awareness and funds that support the Society's extensive services to its members and to the general public. Clearly the fundraising committee is doing a great job, because the National MPS Society provides research funding to a highly significant level. Over $5 million in research grants have been awarded by the National MPS Society since 2001. For example, the Lysosomal Disease Network's protocol number 6703, the groundbreaking MPS I, II and VI longitudinal study led by principal investigator Dr. Elsa Shapiro; and the LDN's Neuroimaging Core have both been generously supported by the National MPS Society.

Importantly, the National MPS Society has a 'Committee on Federal Legislation' that consists of volunteer parents, patients, and Society staff which convenes by monthly conference calls, attends relevant patient

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Meet Our Patient Advocacy Groups

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advocacy meetings in local areas, and educates key decision-makers about MPS and related diseases. The legislative committee tracks, reviews, and supports or opposes legislation important to the MPS and related diseases community. Additionally, the committee reviews governmental agency policies and guidelines that may impact families and individuals with MPS, and strategizes on how to make a positive impact. The committee travels to D.C. annually to advocate with legislators, representatives, health legislative aides, and the National Institutes of Health. Committee members also meet with various governmental decision-makers important for accelerating progress towards treatments and cures, and for protecting the rights of individuals with disabilities. The legislative committee issues a "Call to Action" to all National MPS Society members for each important governmental development requiring the influence of the public—not just in Congress, but in government agencies such as the FDA, the Social Security Administration, the NIH, Health and Human Services, and others. The calls to action currently needing your participation are found at: http://mpssociety.org/legislative-call-to-action/.

The National MPS Society provides extensive multifaceted family support programs for their members. These include: 'Ask the Parents,' an inter-member confidential contact program, wherein National MPS Society member families who have consented to offer themselves to others through email, are connected with other members; a 'Continuing Education Scholarship Program' which offers post-secondary education scholarships for individuals with MPS and related diseases, their siblings under age 30, and their children; 'Extraordinary Experiences' which offers grants of up to $1000 to help individuals aged 13 years and older affected with MPS and related diseases have their own life-enriching extraordinary experience; 'Family Assistance Program' which offers grants for special equipment or medical aids, up to a maximum of $3,000 per 12-month period for parents of an individual with MPS or related diseases, or an adult with MPS or related diseases; 'Medical Travel Assistance Program' which helps fund out-of-town travel costs up to $500 per affected individual per 12 month period, for non-recurring medical appointments more than 200 miles away from the member's home; 'Membership Assistance Program' which waives membership dues for families experiencing financial difficulties, and provides complimentary first year membership to families living in the United States who have a recent diagnosis, and for adults with MPS; the CYCLE program (**C**elebrating **Y**our **C**hild's **L**ife **E**xperiences) acknowledges the families whose loved one has died from MPS. CYCLE conferences are held for bereaved parents. The Society also encourages families to arrange social get-togethers for other families in their region, by offering grants to help assist with event funding. To become a member of the National MPS Society, visit: http://mpssociety.org/become-a-member/.

National MPS Awareness Day was initiated by a Board member of the National MPS Society in 2003 who, because of her children's diagnoses of MPS III, felt that many of the traditional holidays we celebrate were bittersweet, such as birthdays and Mother's Day. She wanted a day to celebrate MPS. The Board subsequently chose February 25th as MPS Awareness Day. According to their official statement, MPS Day began as "a way to honor all of those in the MPS community, to recognize, remember and rejoice in each other. On MPS Day we:

- Remember all the children and adults who suffer from MPS and related diseases.
- Think about the children we have lost.
- Think about the doctors and scientists who are dedicated to finding cures for MPS and related diseases.
- Appreciate each other and are thankful for the strength and support we both give and receive."

On February 16, 2005, the U.S. Senate unanimously approved a resolution designating February 25, 2005 as National MPS Awareness Day. The National MPS Society has successfully received Senate approval for the resolution each year since the initial approval. To help publicize National MPS Awareness Day, the National MPS Society opened the NASDAQ on February 25, 2005.

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Meet Our Patient Advocacy Groups

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On February 25, 2006 the National MPS Society closed the NASDAQ and launched "Join the Search for MPS Patients," an educational campaign to identify and diagnose children who suffer from MPS and related diseases. "Join the Search" is a joint venture among the National MPS Society, BioMarin, Genzyme and Shire. On March 28, 2006, the U.S. House of Representatives approved a resolution to "support the goals and ideals of National MPS Day." This is a permanent resolution.

In 2007 the global MPS advocacy organizations adopted MPS Awareness Day. The date was changed to May 15th, and the name was changed to 'International MPS Awareness Day.' International MPS Awareness Day continues to provide opportunities to enlighten people globally about MPS and related diseases.

The Society is celebrating with its "40 Years of Achievements Gala" on May 2, 2014 in Chapel Hill, NC. This black tie-optional event includes VIP and cocktail receptions, dinner, "Celebration of Heroes," and a live auction. Information is available on the homepage of the Society's Web site, www.mpssociety.org.

Each year, the Society organizes and hosts an Annual National Family Conference that features educational and social events for persons affected by MPS, their families and caregivers. The Lysosomal Disease Network typically provides an educational presentation at each conference, sharing recent research developments and findings in MPS and/or related diseases. The Society also offers a conference scholarship program to enable more persons to attend. This year, the conference will be held at Disney's Contemporary Resort in Orlando, FL from December 18-21, 2014.

The National MPS Society provides the entire world with an inspiring demonstration of what a patient advocacy group can ultimately become, and what it can achieve when thousands work selflessly together for a common goal.

WORLD*Symposium* 2014 -- where the networking was non-stop!

Rare Disease Report is a media partner with the Lysosomal Disease Network

LDN Research *Matters*

Protocol #6717: Clinical and neuropsychological investigations in Batten disease

LDN protocol #6717, entitled "Clinical and neuropsychological investigations in Batten disease," is led by Principal Investigator Jonathan W. Mink, M.D., Ph.D. at the University of Rochester School of Medicine and Dentistry in Rochester, N.Y. Dr. Mink is researching the juvenile form of neuronal ceroid lipofuscinosis, a group of lysosomal diseases collectively known as Batten disease, that cause blindness, seizures, progressive cognitive and behavioral decline, and a movement disorder in children. Dr. Mink created protocol #6717 to continue previous work on a systematic longitudinal natural history study of Batten disease using standardized rating instruments with established inter-rater reliability and validity. Dr. Mink's co-investigators in this include Frederick Marshall, M.D., Erika Augustine, M.D., Heather Adams, Ph.D., Paul Rothberg, Ph.D., Jennifer Kwon, M.D., Christopher Beck, Ph.D., Elisabeth de Blieck, M.P.A., C.C.R.C., and Amy Vierhile, R.N., M.S., C.P.N.P., all at the University of Rochester. The study coordinator is Alyssa Thatcher, B.S. Together, these researchers constitute the "University of Rochester Batten Disease Center Study Group."

The study population for protocol #6717 is any child or young adult with any form of Batten disease who does not have any neurologic disorder other than neuronal ceroid lipofuscinosis, nor any signs or symptoms indicating significant psychological or physical discomfort with the exam process in the opinion of the parent, legal guardian, or examiner. The subject's parent or legal guardian, and the subject's sister(s) are also included in the study population.

The University of Rochester Batten Study Group previously developed the "Unified Batten Disease Rating Scale" (UBDRS), a clinical rating instrument used to assess the severity of physical, behavioral, and seizure symptoms and the functional capabilities of individuals with Batten disease. One of LDN protocol #6717's tasks is to refine and target the UBDRS as a clinical tool and research instrument. Using the UBDRS, study physicians may evaluate participants every year to track disease progression and to determine whether the UBDRS is sensitive to symptom changes. Participants are examined at the University of Rochester Batten Disease Center, or at the Batten Disease Support and Research Association's annual meeting, which is held every summer.

Study personnel may also conduct neuropsychological testing with participants who have Batten disease in order to enhance understanding of their cognitive functioning. Participants with Batten disease may also be asked to have an electrocardiogram (ECG) obtained. This will provide information about cardiac changes that might occur in children with Batten disease.

Additionally, parents or legal guardians of participants with Batten disease may be asked to complete interviews and questionnaires involving the following topics:

- racial and ethnic background, medical history, medications, and symptoms
- family history, parent education, and the type of training the child received when his or her vision began to decline
- previous testing that may have been done to confirm a Batten disease diagnosis
- child's mood and behavior (if child is 5 - 18 years old)
- parental beliefs regarding the placement of pacemakers
- parental beliefs regarding procedures and other surgeries for children with Batten disease
- parental opinions regarding supportive care during the various stages of Batten disease.

If genetic testing has not yet been done, blood or cheek cells may be collected to confirm a Batten disease diagnosis. Blood and cheek samples from participants with Batten disease and their parents may also be collected and used in an attempt to better understand the genetic changes that cause Batten disease and influence its severity. Furthermore, female siblings may participate by providing a blood sample. These samples will be examined to see how the amount of estrogen in the blood of females with Batten disease compares to the amount of estrogen in

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the blood of their sister who does not have Batten disease.

Participants will be added to a database of children with Batten disease whose parents have consented to be contacted about possible participation in future studies. This registry serves as a vehicle for recruitment. More information is available about this study on ClinicalTrials.gov by searching for study NCT01873924.
Visit: http://clinicaltrials.gov/ct2/search/index.

Selected publications associated with LDN protocol number 6717:

H.R. Adams, K. Rose, E.F. Augustine, J.M. Kwon, E.A. Deblieck, F.J. Marshall, A. Vierhile, J.W. Mink, M.A. Nance, Experience, knowledge, and opinions about childhood genetic testing in Batten disease. Mol Genet Metab 111(2) (2014)197-202. PMCID: PMC3919022.

A. Schulz, A. Kohlschütter, J.W. Mink, A. Simonati, R. Williams, NCL diseases - clinical perspectives. Biochim Biophys Acta 1832(11) (2013) 1801-1806. PMID: 23602993.

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S.B. Dolisca, M. Mehta, D.A. Pearce, J.W. Mink, B.L. Maria, Batten disease: clinical aspects, molecular mechanisms, translational science, and future directions. J Child Neurol 28(9) (2013) 1074-1100. PMID: 23838031.

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J. Cialone, H. Adams, E.F. Augustine, F.J. Marshall, J.M. Kwon, N. Newhouse, A. Vierhile, E. Levy, L.S. Dure, K.R. Rose, D. Ramirez-Montealegre, E.A. de Blieck, J.W. Mink, Females experience a more severe disease course in Batten disease. J Inherit Metab Dis 35(3) (2012) 549-555. PMCID: PMC3320704.

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J.M. Kwon, H. Adams, P.G. Rothberg, E.F. Augustine, F.J. Marshall, E.A. de Blieck, A. Vierhile, C.A. Beck, N. Newhouse, J. Cialone, E. Levy, D. Ramirez-Montealegre, L.S. Dure, K.R. Rose, J.W. Mink, Quantifying physical decline in juvenile neuronal ceroid lipofuscinosis (Batten disease). Neurology 77(20) (2011) 1801-1807. PMCID: PMC3233207.

J. Cialone, E.F. Augustine, N. Newhouse, A. Vierhile, F.J. Marshall, J.W. Mink, Quantitative telemedicine ratings in Batten disease: implications for rare disease research. Neurology 77(20) (2011) 1808-1811. PMCID: PMC3233206.

J. Cialone, E.F. Augustine, N. Newhouse, H. Adams, A. Vierhile, F.J. Marshall, E.A. de Blieck, J. Kwon, P.G. Rothberg, J.W. Mink, Parent-reported benefits of flupirtine in juvenile neuronal ceroid lipofuscinosis (Batten disease; CLN3) are not supported by quantitative data. J Inherit Metab Dis 34(5) (2011) 1075-1081. PMCID: PMC3174318.

P.I. Dickson, A.R. Pariser, S.C. Groft, R.W. Ishihara, D.E. McNeil, D. Tagle, D.J. Griebel, S.G. Kaler, J.W. Mink, E.G. Shapiro, K.J. Bjoraker, L. Krivitzky, J.M. Provenzale, A. Gropman, P. Orchard, G. Raymond, B.H. Cohen, R.D. Steiner, S.F. Goldkind, R.M. Nelson, E. Kakkis, M.C. Patterson, Research challenges in central nervous system manifestations of inborn errors of metabolism. Mol Genet Metab 102(3) (2011) 326-338. PMCID: PMC3040279.

H.R. Adams, C.A. Beck, E. Levy, R. Jordan, J.M. Kwon, F.J. Marshall, A. Vierhile, E.F. Augustine, E.A. de Blieck, D.A. Pearce, J.W. Mink, Genotype does not predict severity of behavioural phenotype in juvenile neuronal ceroid lipofuscinosis (Batten disease). Dev Med Child Neurol 52(7) (2010) 637-643. PMCID: PMC2895016 .

Meet the Principal Investigators

Jonathan W. Mink, M.D., Ph.D. is the Principal Investigator of the Lysosomal Disease Network protocol number 6717 entitled "Clinical and neuropsychological investigations in Batten disease." Dr. Mink holds the Frederick A. Horner, M.D. Endowed Professorship in Pediatric Neurology; and is Professor in Departments of Neurology, Brain & Cognitive Sciences, Neurobiology & Anatomy, and Pediatrics, all at University of Rochester in Rochester, New York. Dr. Mink is a pediatric neurologist who specializes in

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movement disorders that begin in childhood. As a movement disorders specialist, Dr. Mink cares for children with a variety of conditions that impair voluntary movements, cause involuntary movements, or both. Such conditions include dystonia, chorea, tics, myoclonus, tremor, stereotypies, Parkinsonism, and combinations of these such as may occur in conditions like cerebral palsy. In addition to movement disorders, neurodegenerative diseases are also a focus of his clinical practice and research. One of Dr. Mink's neurodegenerative disease research interests is juvenile neuronal ceroid lipofuscinosis (Batten disease). His research has focused on the natural history of the disease, and is now pursuing potential disease-modifying therapeutics.

In addition to his clinical practice and research, Dr. Mink is the Chief of Child Neurology and the Vice Chair of Neurology at the University of Rochester. He is director of the Batten Disease Support and Research Association (BDSRA) "Batten Disease Center of Excellence" at the University of Rochester. He serves on a number of advisory boards including the Tourette Syndrome Association, the NINDS Advisory Council, the Pediatric Advisory Committee of the FDA, and the BDSRA (see the BDSRA article on page one of the December 2013 issue of '**Indications**'). He is also an associate editor of *Neurology*. To learn more about Dr. Mink, please visit his University of Rochester health care provider page at: http://www.urmc.rochester.edu/people/23513877-jonathan-w-mink/researchers.

Selected Jonathan Mink Publications:

K.J. Black, A.Z. Snyder, J.W. Mink, V.N. Tolia, F.J. Revilla, S.M. Moerlein, J.S. Perlmutter, Spatial reorganization of putaminal dopamine d2-like receptors in cranial and hand dystonia. PLoS One 9(2) (2014) e88121. PMCID: PMC3919754.

H.M. Tully, J.C. Dempsey, G.E. Ishak, M.P. Adam, J.W. Mink, W.B. Dobyns, S.M. Gospe Jr., A. Weiss, J.O. Phillips, D. Doherty, Persistent figure-eight and side-to-side head shaking is a marker for rhombencephalosynapsis. Mov Disord 28(14) (2013) 2019-2023. PMID: 24105968.

J.W. Mink, Conversion disorder and mass psychogenic illness in child neurology. Ann N Y Acad Sci 1304 (2013) 40-44. PMID: 24138153.

Check Your Knowledge of Lysosomal Diseases

How well do you know Batten disease?

By Evelyn S. Redtree, M.S.

The neuronal ceroid lipofuscinoses are generally known in North America—collectively—as Batten disease. (Originally Batten disease was the name only for juvenile neuronal ceroid lipofuscinosis.) The various forms of childhood-onset neuronal ceroid lipofuscinoses (NCL) are classified by age of onset. They have the same basic progression and outcome, but each is the result of a different genetic defect. Most of these genetic defects code for lysosomal enzymes, but some of them code for transmembrane proteins, localized to the lysosomes. In many cases, the function of these transmembrane proteins hasn't yet been discovered. The progression of the disease, common to all the childhood-onset types, is as follows: over time, affected children suffer progressive loss of sight and motor skills, worsening mental impairment, and worsening seizures. Eventually, children with NCL become blind, bedridden, unable to communicate, and ultimately die as a result of life-threatening complications of the disease.

Inheritance Patterns

In childhood-onset forms, NCL is inherited in an autosomal recessive pattern. In adult-onset forms (adult NCL, or ANCL), Kufs disease is inherited in an autosomal recessive manner, while Kufs disease-Parry type is inherited in an autosomal dominant manner.

Incidence

NCL is thought to occur in an estimated 2 to 4:100,000 births in the United States. NCL disorders are more frequent in some Scandinavian countries, due to founder effect. The founder effect refers to random variation in the frequency of rare genes during the formation of a new subpopulation of limited size. If the founders forming the subpopulation included a member with a rare recessive allele, the frequency of this allele will be much higher within the subpopulation than outside it. In Finland, for example, the

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incidence of NCL is estimated to be 10:100,000; in Iceland, the estimate is 7:100,000. In comparison, in Germany the incidence is estimated to be 1.2: 100,000; and in Sweden, the estimated incidence is 3:100,000.

Forms of NCL

There are numerous types and type-variants of the neuronal ceroid lipofuscinoses, each having a different cytogenetic location. To explore these many variants, a search for 'neuronal ceroid lipofuscinosis' in the "Online Mendelian Inheritance in Man®" Web site is recommended. Visit: http://www.omim.org/. Several of the more frequently diagnosed forms of NCL are:

Infantile neuronal ceroid lipofuscinosis, also known as Santavuori-Haltia disease, or INCL, can have its onset from 6 months to 2 years of age, with rapid progression; an average lifespan is 9 to 11 years. Clinical features include: failure to thrive, progressive postnatal microcephaly, epilepsy, myoclonus, regression of psychomotor development, progressive vision loss with optic atrophy, retinal degeneration, macular degeneration, and progressive deterioration of speech with ultimate speech loss. The cytogenetic location is 1p32.

Late infantile neuronal ceroid lipofuscinosis, also known as Jansky-Bielschowsky disease, or LINCL, can have its onset from 2 to 4 years of age, with rapid progression; an average lifespan is 10 to 15 years. Clinical features include: progressive vision loss, retinal degeneration, developmental regression, speech and language difficulties, seizures, ataxia, myoclonus, neurophysiologic abnormalities (EEG, VEP, SEP), and cerebral atrophy. Under ultraviolet microscopy, autofluorescent lipopigment is seen in neurons. The cytogenetic location is 11p15.4.

Juvenile neuronal ceroid lipofuscinosis, also known as Batten disease, Spielmeyer-Vogt-Sjögren-Batten disease, or JNCL, can have its onset from 4 to 10 years of age. The average lifespan is from 20 to 40 years. Clinical features include: progressive vision loss with ultimate blindness, retinitis pigmentosa, macular degeneration, optic atrophy, psychomotor degeneration, mental retardation, dementia, extrapyramidal signs, myoclonus, Parkinsonism, cerebellar signs, progressive inability to walk, seizures, dysarthria, and cerebral atrophy. Under ultraviolet microscopy, autofluorescent lipopigment is seen in neurons. The cytogenetic location is 16p11.2.

Adult NCL, also known as ANCL, and as Kufs disease, or Kufs disease-Parry type (depending upon the manner of inheritance) is a neurodegenerative disorder without retinal involvement. Kufs disease is classified as ANCL phenotype A. Its onset is in adulthood (third to fourth decade). Clinical features include: seizures, cerebellar ataxia, pyramidal and extrapyramidal signs, myoclonus, progressive myoclonic epilepsy, dementia, cerebral atrophy, and leukoencephalopathy found on CT and MRI. Auditory and visual hallucinations have also been reported. Under ultraviolet microscopy, autofluorescent lipopigment in neurons is seen. The cytogenetic location is 15q23.

Kufs disease-Parry type has an onset in adulthood (third to fourth decade), and it is rapidly progressive. It is classified as ANCL phenotype B. Clinical features include: usually non-progressive epileptic seizures, dementia, speech deterioration, myoclonus, cerebellar signs, cerebellar ataxia, possible Parkinsonism, facial dyskinesia and extrapyramidal signs. Under ultraviolet microscopy, autofluorescent lipopigment is seen in neurons. The cytogenetic location is 20q13.33.

Northern epilepsy with mental retardation, also known as EPMR, can have its onset from 5 to 10 years of age. The disease is slowly progressive with a protracted course. Clinical features include: seizures with onset at age 5 to 10 years, with increasing seizure frequency approaching puberty, then decreasing seizure frequency in middle age; generalized tonic-clonic seizures; complex partial seizures; EEG abnormalities; mental deterioration beginning 2 to 5

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years after onset of seizures; mental retardation by age 30 years; clumsiness noticed in early adulthood; difficulties with equilibrium; progressive cerebral atrophy; progressive cerebellar atrophy; and behavioral irritability beginning at puberty. Under ultraviolet microscopy, autofluorescent lipopigment is seen in neurons. All known cases are caused by a Finnish founder mutation in the CLN8 gene. The cytogenetic location is 8p23.3.

Treatment

Treatment is supportive only and consists of palliative care with administration of anticonvulsive drugs, as well as educational, psychological, and psychiatric management. Supportive services from NCL patient advocacy groups are available in some countries. In the United States, the BDSRA supports families and patients (see '**Indications**' cover article about the BDSRA, in Vol. 1 No. 1, available at LysosomalDiseaseNetwork.org).

Calendar of Upcoming Events

National Tay-Sachs and Allied Diseases 36th Annual Family Conference, April 3 - 6, 2014 in Atlanta, GA, USA. Registration deadline was March 7th. Visit: http://www.ntsad.org/index.php/general-information.

National MPS Society's "40 Years of Achievements Gala," May 2, 2014 in Chapel Hill, NC, USA, at the Carolina Inn. "Gala" rates at 3 hotels; hotel reservation deadline is April 9th. More information is available at: http://mpssociety.org/posts/uncategorized/40-years-of-achievements-gala-invitation/.

The Canadian MPS Society's 30th Anniversary National Family Conference, July 25 - 27, 2014 in Calgary, Alberta, Canada. For more information, visit: https://www.mpssociety.ca/page/events.aspx.

Batten Disease Support & Research Association Annual Family Conference, July 24 - 27, 2014 in Columbus, OH, USA. Conference convenes at the Columbus Airport Marriott. The BDSRA homepage features an events listing. Visit: http://www.bdsra.org/. They also have a Facebook page with the conference name: Camp Columbus.

13th International Symposium on MPS & Related Diseases, August 13 - 17, 2014 in Costa do Sauipe, Bahia State, Brazil. For more information, visit: http://www.mps2014.com/new/.

36th Annual AGSD Family/Medical Conference, September 19 - 20, 2014 in Dearborn, Michigan, USA at Doubletree by Hilton Hotel Detroit-Dearborn. For more information, visit: http://www.agsdus.org/html/2014conference.html.

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/.

"360º 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. Abstract submission deadline: June 20, 2014. For more information, visit: http://www.febs-lysosome.org/.

National MPS Society Annual National Family Conference, December 18 - 21, 2014 at Disney's Contemporary Resort in Orlando, FL, USA. For more information, visit: www.mpssociety.org.

Indications™

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