Indications™

Newsletter of The Lysosomal Disease Network™

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Meet Some MPS Societies Serving Outside of the United States

By Evelyn S. Redtree, M.S.

In past issues of "**Indications**," groups dedicated to serving the needs of mucopolysaccharidosis patients have been featured. In April 2014 we featured the National MPS Society (www.mpssociety.org); and in December 2014 we featured The Ryan Foundation for MPS Children (http://ryanfoundation.net/home/). In this issue, we will also look at some of the MPS patient advocacy groups in some other English-speaking nations.

Before we do that, let us learn what recent developments are happening at America's National MPS Society, founded in February 1974. The National MPS Society's Executive Director Barbara Wedehase, MSW, CGC, who has been the Executive Director of the National MPS Society since 2000, had previously announced her intention to retire, and a search was underway for a new Executive Director. It has been announced that upon Barbara's retirement, Mark Dant will take up this critically important position. Mark, who is the Executive Director and co-founder of The Ryan Foundation for MPS Children, has decades of experience in highly active leadership in the MPS world community. The LDN congratulates the MPS Society in choosing Mark Dant as its new Executive Director-to-be.

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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 . . .

http://MLDfoundation.org

By Evelyn Redtree, M.S., and Teryn Suhr

The March 2015 issue of "**Indications**" focused on metachromatic leukodystrophy (MLD) in 'Check Your Knowledge' (on page 6). Due to space constraints, the MLD Foundation was not profiled in that issue. We invite you to refresh your awareness of that issue, and now enjoy learning about the MLD Foundation in this issue of "**Indications**."

The MLD Foundation was founded in May 2001 to serve families throughout the world affected by metachromatic leukodystrophy. This was the result of the 7 year diagnostic odyssey taken by Dean and Teryn Suhr

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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.

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The MLD Foundation

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of West Linn, Oregon, that culminated in their oldest daughter, Lindy, being diagnosed with MLD in 1995 and their youngest daughter, Darcee, undergoing a bone marrow transplant and passing away from complications. At that time Lindy was too far progressed to have any treatment. The late Dr. William Krivit, physician, researcher, professor and co-founder of the University of Minnesota's Blood and Marrow Pediatric Transplant program, was an important catalyst in the formation of the MLD Foundation, and a strong advocate of their efforts, methods, goals, and direction.

Dean Suhr is President and Board Chair, and Teryn Suhr is Executive Director of the MLD Foundation. There is a five-person Fiduciary Board and an eight-member Medical and Scientific Advisory Board comprised of global experts in MLD. The MLD Foundation is a 501(c)(3) non-profit US tax- exempt organization.

Compassion in Practice

The MLD Foundation has identified its purposes as facilitating compassion, increasing awareness, influencing research, and promoting education. To facilitate compassion, it hosts (under its "MLD Family™" paradigm) periodic MLD Family Conferences™ and MLD Family Gatherings™, including some meeting sites outside of the U.S., where families—many for the first time—can meet other MLD-affected families face to face. Together they absorb research and therapy updates from some of the world's leading MLD doctors, researchers and scientists. These gatherings have been generously funded by individual donors, family-foundation donors, and the pioneering pharmaceutical corporation Shire. When the conference is ongoing, it is presented on the MLD Foundation's Web site as a live-streaming Webcast for anyone who is interested. Videos of past meetings, beginning with 2012, are also available (http://mldfoundation.org/mld-videos.php).

Participants enjoy the 2015 MLD Family Conference™ in Newark, Delaware, which convened July 10-11. Photo by Levi Gershkowitz (visit Living in the Light at http://www.frompatienttoperson.com)

Attendees at the 2015 MLD Family Conference™ in Newark, Delaware increased their scientific knowledge about MLD via numerous presentations provided by MLD experts.

The MLD Foundation also hosts an online private primary caregiver Family Discussion List where 300 families on the MLD journey from around the world gather to share their daily challenges, needs and experiences, and to support one another. The key criterion to join this list is direct involvement in the care of an MLD-affected individual.

Additionally, the MLD Foundation hosts an online Extended Friends and Family Discussion and Support e-mail list ("EFF") that is targeted at extended family members and friends of families affected by MLD. The EFF is for those who want to learn from each other how to best engage with the primary caregivers and families affected by MLD.

Another compassionate service provided by the MLD Foundation is The MLD Family Compassion Fund™ that exists thanks to a partnership and generous grant from the "Believing for Bryleigh Foundation" (http://believe4b.com/). Family Compassion Fund grants are made to improve the quality of life for an MLD-affected loved one, and are determined based on need, family access to other resources, the number of applications re-

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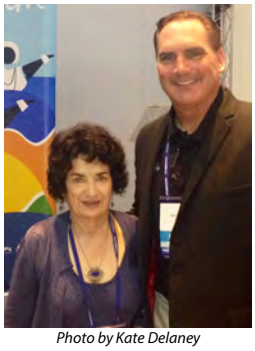

Photo by Kate Delaney

Elsa G. Shapiro, Ph.D. and Mark Dant of The Ryan Foundation for MPS Children at the 13th International Symposium on MPS & Related Diseases in Costa do Sauipe, Bahia State, Brazil, in 2014. For years, the MPS Society and The Ryan Foundation have generously supported Dr. Shapiro's ground-breaking MPS research, LDN Protocol #6703. This study is now led by Dr. Chester Whitley, Principal Investigator of the LDN.

This year, the National MPS Society is hosting its 29th Annual Family Conference in Salt Lake City, UT from Sept. 17–19. Due to there being many companies with FDA-approved treatments for MPS diseases that are either in clinical trials now, or are moving toward clinical trials in the next 12–24 months, the Society has arranged for representatives from these companies to be available for an "open house" during the Annual Family Conference. This will allow meeting attendees to personally talk with these representatives and hear firsthand about new treatments, many of which are focused on treating the central nervous system.

Dr. Laurie Muldowney, medical officer for the FDA's Center for Drug Evaluation and Research ("CDER"), will speak on Friday Sept. 18th about the FDA approval process for new treatments. Additionally, a member family will discuss their experience in participating in a clinical trial. (For more information about the CDER, read the review of a talk presented by Richard A. Moscicki, M.D., Deputy Center Director for Science Operations at the CDER, in the March 2014 issue of "**Indications**," pages 7 and 11.)

You still have time to make your arrangements to attend the 29th Annual Family Conference; hotel and conference reservation deadlines are August 27, 2015. For more information about this exciting conference, and to register, visit: www.etouches.com /MPS2015.

The Canadian Society for Mucopolysaccharide & Related Diseases Inc.

The Canadian Society for Mucopolysaccharide & Related Diseases Inc., often referred to as the Canadian MPS Society (www.mpssociety.ca), is led by Executive Director Jamie Myrah. The Society, founded in 1984, operates programs that include financial assistance to their member families through its Family Assistance Program (FAP). Canadian resident member families are eligible for up to $1,500.00 in funding per year, and up to a maximum of $3,000.00 in funding over a five-year period. Among other things, these funds can be used to help provide respite care.

The Society endeavors to help MPS families connect with one another, for instance through local gatherings and its Family Referral Directory. Its National Family Conference, held every two years, gives affected families and medical professionals an opportunity to learn more about new research, treatments and care strategies, to meet and share information and experiences with each other, and to form and strengthen friendships. The most recent National Family Conference convened in July 2014, celebrating the Canadian MPS Society's 30th Anniversary. In 2008 the Society also hosted the 10th International Symposium on MPS & Related Diseases in Vancouver.

Jamie Myrah
Executive Director

The Society has many educational outreach products, such as its exceptionally outstanding "Family Resource Binders" for MPS I, II, IV and VI, that are available as hard copies at no charge to Society members affected by these diseases, and available online for download (http://www.mpssociety.ca/page/family%20resource%20binders.aspx). It also publishes

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ceived, the Family Compassion Fund balance and its anticipated donations. All applications are reviewed for completeness and clarity, then de-identified and sent to the MLD Family Compassion Fund Review Committee, which consists of 5 independent arms-length reviewers with medical, family, economic and at-large perspectives. At this time, applications are accepted only for U.S. residents. Wisely, Compassion Fund payments are generally made directly to a medical or other service provider to pay a bill, and generally not to the family making the Compassion Fund grant request. This avoids any issues with reporting income or gifts to social service agencies that might lead to a reduction in government service benefits or payments, while preventing misperceptions about appropriate use of funds.

Promotion of MLD Awareness

To increase awareness of metachromatic leukodystrophy throughout the medical, scientific, educational, and counseling community, the MLD Foundation encourages its members to be proactive with educational outreach to every professional person they interact with. Members are also encouraged to contact their local media, so that their story of living with MLD in the family can appear in press, on television, and local radio. The goal is to increase the public's awareness so that no one affected by MLD is misdiagnosed or diagnosed too late for any effective long-term therapy.

Research for Treatment and a Cure

In pursuit of their purpose of influencing research, the MLD Foundation strongly believes that influencing research, combined with funding research, provides the optimal environment for meaningful and successful MLD research. They believe that influencing research means to expand the scope of existing research to include MLD-specific components, as well as to influence funding so that MLD-specific research can be started and continued.

The MLD Foundation is currently working with researchers at the University of Washington to develop a viable newborn screen for MLD. It is also working with industry leaders to facilitate a better understanding of the MLD journey, burden of care, and cost of care. It is also providing input to clinical trial design, and helping to populate clinical trials. Advocating for MLD families and pushing research forward is always at the top of the MLD Foundation's priorities.

For more about Dr. Gelb: https://depts.washington.edu/chem/people/faculty/gelb.html.

Teryn Suhr and Dr. Michael Gelb in his chemistry lab, talking about the technique he is developing for creating a newborn screen for MLD. Dr. Gelb is Professor, and Boris and Barbara L. Weinstein Endowed Chair in Chemistry, and Adjunct Professor of Biochemistry, in the Departments of Chemistry and Biochemistry, University of Washington in Seattle.

Education about MLD

The MLD Foundation promotes education at its MLD Family Conferences™ and MLD Family Gatherings™, where multiple factual presentations are given, often while being live-streamed online. Its Web site also provides "MLD 101," where information appropriate for the general public is presented (http://mldfoundation.org/mld-101-what.html). There is also a large assortment of educational videos at the MLD Foundation Web site, with acclaimed presenters such as Dr. Marc Patterson, Dr. Alessandra Biffi and Dr. David Wenger (http://mldfoundation.org/mld-videos.php).

One-Stop Shop

The MLD Foundation Website is an excellent source of information about MLD, its management, treatment possibilities and clinical trials, and family engagement opportunities. It certainly is the go-to site for all concerns arising from a diagnosis of metachromatic leukodystrophy. If you have high-level Web site management skills and would like to volunteer; would like to create a fundraiser of your own; or would like to donate, be sure to visit their Web site for specific information about these special current needs.

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a variety of superb, downloadable educational booklets relating to MPS and its management (http:// www.mpssociety.ca/page/mps%20booklets.aspx), and a periodic newsletter. Several educational videos are viewable at its Web site, as well as a wealth of informative Web pages about MPS diseases. Additionally, the Society has created a physician-education outreach effort called "Join the Search for MPS" (http://www.jointhesearch.ca/) to help Canadian physicians recognize MPS diseases in their patients, appropriately refer them for genetic analysis, and provide them with appropriate patient education and medical interventions.

Canadian MPS Society Board Director Melissa Bilodeau and Bernie Geiss, Board Chair, had a blast at the 3rd Annual "Cove Fun 5k for MPS," held April 26, 2015 in North Vancouver, BC, Canada.

The Society for Mucopolysaccharide Diseases, in the U.K.

Founded in 1982, the Society for Mucopolysaccharide Diseases (the MPS Society) in the United Kingdom (www.mpssociety.org.uk) is led by Chief Executive Christine Lavery. In 1988, with a grant of over £120,000, the Society helped to establish the first specialist team dedicated to the clinical management and treatment of MPS and related diseases at the Royal Manchester Children's Hospital, led by Professor Ed Wraith. With this investment, the MPS Specialist Outreach Clinics were born. Families and individuals living with MPS no longer faced arduous journeys to Manchester. Instead, they visited specialist metabolic doctors in Belfast, Glasgow, Cardiff, Newcastle, Birmingham, Cambridge and Bristol.

Over the last 30 years, the MPS Society has invested overall £5 million developing the best care for children and adults diagnosed with mucopolysaccharide and related lysosomal diseases, and funding research that may lead to the development of new therapies. In 2006 the MPS Society invested £1.3 million in the establishment of the MPS Stem Cell Group at the University of Manchester, led by Dr. Brian Bigger. Currently this important academic group is developing gene therapy for MPS II, IIIA, and IIIB. The group also works with Dr. Simon Jones at the Manchester Children's Hospital in the genistein aglycone clinical trial for MPS IIIA, partially funded with a grant of £600,000 from the MPS Society. For more information about these efforts in Manchester, see page 9 in the May 2015 issue of "**Indications**."

The MPS Society is a member of NHS* England's "Expert Advisory Group for Lysosomal Storage Diseases" and works with health commissioners and government to set national standards on clinical care and treatment for those with MPS, Fabry disease, and related lysosomal diseases across the UK.

Patient Access to Clinical Trials

Learning from the MPS Society members' experience of participation in two early clinical trials for enzyme replacement, in 2006 the MPS Society launched its "Clinical Trial Patient Access Programme." The key objectives of this program, supported by clinicians and the pharmaceutical industry alike, are to provide enhanced logistical support, including risk management, organizing disability-sensitive accommodation and travel; and timely reimbursement of expenses. Since 2006 the MPS Society has supported children and adults and their families on nearly 20 studies with durations of up to four years, at specialist centers in the UK, Europe and the USA.

*National Health Service in Great Britain

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30 years of MPS Patient Data

"The MPS Society Registry" is an on-going database that tracks demographic data, treatment options, some natural history data and patient-reported outcomes from over 1300 children and adults with MPS in the UK, and several thousand in the rest of the world. It was initiated by the founding Board of the MPS Society over thirty years ago. As visionary as that decision was, little could those Trustees have foreseen how valuable this MPS Registry would prove decades later! In the last 13 years with enzyme replacement therapy being clinically trialed and considered for marketing approval for MPS I, MPS II, MPS IVA and MPS VI, the MPS Society Registry has presented the most complete data set available worldwide. Even though there are now product-based registries for Fabry disease, MPS I, MPS II and MPS VI, the MPS Registry continues to serve the MPS community. Its data sets have been used for informing patients about clinical trial and focus group opportunities; supporting the pharmaceutical industry in new clinical trial development; and advising Healthcare Commissioners and payers on patient cohorts.

International Meeting Origination

In 1990 the MPS Society hosted the first "International Symposium on Mucopolysaccharide Diseases" at the University of Manchester Institute of Science and Technology. Over 600 patients, their families, clinicians, researchers and scientists participated in this three-day meeting that boasted a comprehensive, volunteer-led children's activity program to enable parents to attend the symposium. This meeting continues to be held every two years around the world.

Challenging Bad NHS Decisions

In April 2005 the highly-specialized "Service for Lysosomal Storage Diseases" was nationally designated by the Department of Health in the UK. Establishment of a nationally designated service, including both clinical management and treatment, was not only vital for UK MPS patients, but continues to influence medical policy decisions in Europe and beyond. This national designation was achieved only after eighteen months of lobbying by MPS members and the MPS Society, in tandem with its advocacy team supporting families to appeal decisions by NHS Primary Care Trusts to ***not prescribe*** life-saving enzyme replacement therapy for MPS I. In addition, the MPS Society's advocacy team helped bring two such decisions to judicial review.

Not complacent, in 2013 when the new "Health and Social Care Act" became law, and the Advisory Group for Nationally Specialized Services was to be disbanded, the MPS Society supported over 400 member families to set out their concerns to the Prime Minister, Deputy Prime Minister, and their Members of Parliament. MPS Society Chief Executive Christine Lavery said, "today in 2015 the people of the U.K. have seen the damage of this extraordinary discriminatory legislation, which has left children and adults with MPS IVA [Morquio syndrome type A] without access to enzyme replacement therapy, 14 months after it received marketing approval in the USA and Europe." Elosulfase alfa (Vimizim®, made by BioMarin Pharmaceutical Inc.) is the only ERT to address the cause of MPS IVA. There are about 35 U.K. children who, because they had participated in a clinical trial, were supplied with Vimizim® by the manufacturer on a compassionate basis.[1] This largesse ended late June 2015.[1]

On July 2, 2015, NHS England announced it has ***declined to fund*** the cost of the drug — around £400,000 annually per patient — and referred the matter to a cost-effectiveness analysis by the U.K.'s National Institute of Health and Care Excellence.[1] On that same day, NHS England also announced it will ***not*** fund sapropterin dihydrochloride (Kuvan®), a designated orphan drug which received approval in the European Union in December 2008 for treatment of the inherited, rare metabolic disorder phenylketonuria (PKU) in children.[1]

The MPS Society's superb summer 2015 newsletter provides details about its vigorous response to these unacceptable actions by NHS England. You can

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download it from a link (shown in blue) located at: http://us9.campaign-archive1.com/?u=3a7f2428dd46eff590fccf83b&id=6c8adbb2ea&e=b9dd882a95.

The MPS House

Remarkably, the Society operates MPS House, a national source of authoritative advice and information, a place where learning and teaching about MPS and related lysosomal diseases can be shared, and a focal point for the UK-wide MPS Society. The MPS House provides ample space for the Society to provide all of its advocacy and support services, as well as a modest conference area and training resource, plus library area. The library houses a range of publications and resources on all aspects of rare genetic diseases, lysosomal diseases, working in the voluntary sector, and charitable organization management. MPS House is ideally situated for motorway access and public transport to all parts of the United Kingdom as well as to London, Heathrow and Luton airports. The center is fully accessible to visitors, who receive a warm welcome whether contacting MPS Society remotely, or visiting MPS House in-person.

The International MPS Network

The MPS Society (UK) is also the Secretariat for the International MPS Network (http://www.impsn.org/), which was established by the MPS Society (UK) in 1984. The International MPS Network defines itself as "the official body of the patient associations representing MPS and MPS Societies at a European and global level." Membership is only open to the one nationally-recognized MPS Society or relevant patient association for each country globally. Up to two representatives from each accepted MPS Society or relevant patient association may attend the International MPS Network Meetings. Observers and translators may attend by prior agreement with the MPS International Network. The International MPS Network meets at least annually, and where the opportunity presents itself, twice a year. One of the goals of each meeting is to ensure that critical scientific and treatment information is shared both among and within countries, and with their MPS patients. There is no membership fee; however, member organizations are responsible for meeting the costs of their representatives' attendance, if this is not covered by the organization hosting the meeting.

Participating MPS societies include those representing the U.S., Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Estonia, France, Germany, Hong Kong, Hungary, Italy, Japan, the Netherlands, New Zealand, Norway, Poland, the Republic of Ireland, Russia, Serbia, Spain, Sweden, Switzerland, Taiwan, Turkey and the United Kingdom.

The priorities of the International MPS Network include: (1) acting as an independent forum for MPS societies and relevant patient associations at a European and global level, including supporting each other and assisting emerging new MPS patient organizations; (2) promoting the well-being of those affected by MPS and related lysosomal diseases through the best practices of clinical diagnosis, management and treatment; (3) promoting public and professional awareness of MPS and related lysosomal diseases; (4) identifying research priorities and potential collaborations, and where appropriate, working in partnership with the academic community and the pharmaceutical industry; (5) developing relationships and partnerships with other lysosomal disease groups for the purposes of collaboration and joint learning; and (6) overseeing the nominations of an MPS society or relevant patient association to host the "International Symposium on Mucopolysaccharide Diseases" mentioned above; and presiding over the decision making, forward planning and reporting of these biannual symposia.

Irish Society for Mucopolysaccharide Diseases

Founded in 1995 and located in the Republic of Ireland, the Irish Society for Mucopolysaccharide Diseases (www.mpssociety.ie) is a voluntary support group that represents and supports children and adults suffering from MPS and related diseases, their families, caregivers, and their medical and supporting professionals. The aims of the Society are: (1) to act as a support network for those affected by MPS and related diseases; (2) to encourage more public awareness of

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MPS and related diseases; and (3) to promote and support research into MPS and related diseases. In support of these aims, the Irish MPS Society holds an annual "All Ireland Conference," including speakers and special events. The MPS Society also provides both general and practical support to those who are affected by the MPS diseases — both patients and their families. This includes informal and social contacts such as "MPS family weekends," providing educational information, providing research funding grants (http://www.mpssociety.ie/wordpress/?page_id=29), and sharing practical steps to improve the daily life of those affected by the MPS diseases. The Society also helps its members participate in international lysosomal disease conferences.

Mucopolysaccharide & Related Diseases Society Australia Ltd.

Mucopolysaccharide & Related Diseases Society Australia Ltd. (the MPS Society) (www.mpssociety.org.au) is led by its National Manager Nicole Millis, parent of a child with Hunter syndrome (MPS II). The Society defines itself as more than a support group for parents — its mission and vision statements include "we value, nurture and support all those who are affected directly or indirectly by mucopolysaccharide and related disorders." They aim to support their members, promote partnerships with professionals, and promote community awareness of MPS and its impact on families and caregivers.

This Society was founded in November 1983 by parents of MPS children. From the beginning, they established strong contacts with the MPS Society in the UK. Founding members attended UK MPS Society conferences and other international MPS society conferences, and gradually developed the ability to originate and run highly successful MPS society conferences, MPS family days, and MPS information days in Australia. Additionally, the 2010 International Symposium on MPS & Related Diseases also convened in Adelaide, South Australia. A total of 14 national conferences have convened in Australia so far, with the most-recent national conference held in April 2015.

The Society also provides its "MPS Assistance Program." Through it the Society provides funding for one-time expenses related to MPS. Such a grant may be used to purchase equipment and services that other programs may not fund, or fail to fully fund. The Society's Web pages also provide highly-detailed information for families about how to proceed in seeking to obtain every conceivable type of assistance provided by their local, state and national governments. In a nation so huge, and as sparsely-populated as much of Australia is, this online information often makes a huge impact on individuals and their caregivers.

The combined dedication, creativity, and labor of these societies — and their comrades in many non-English-speaking countries — prove that MPS patients, their families and caregivers truly are movers and shakers who improve human lives on a global scale. It is no wonder that these MPS societies receive maximum respect within the world's rare diseases community!

Reference cited:

[1]*The Guardian* online newspaper: accessed July 2, 2015. "NHS England says no to Morquio drug, passing decision to watchdog." http://www.theguardian.com/society/2015/jul/02/nhs-england-no-to-morquio-drug-decision-watchdog-nice

Ohio Advances, Keeping Pace with Its Neighbor to the East

On June 30, 2015, the Governor of Ohio signed into law Krabbe disease newborn screening for the State of Ohio, which will take effect for all Ohio babies born after 7-1-2016. Multiple Ohio families with Krabbe disease-affected children joined forces with Ohio State Senator Keith Faber, the bill's sponsor, to achieve this outcome. Does YOUR state screen all newborns for Krabbe disease? What about other lysosomal disease screenings in your state? Learn more: http://www.babysfirsttest.org/newborn-screening/states.

LDN Research *Matters*

Longitudinal study of bone and endocrine disease in children with MPS I, II and VI: A multi-center study of the Lysosomal Disease Network

By Evelyn S. Redtree, M.S. and Lynda Polgreen, M.D., M.S.

The current LDN research project entitled "Longitudinal study of bone and endocrine disease in children with MPS I, II and VI: A multi-center study of the Lysosomal Disease Network" is a continuation of LDN Protocol # 6705, which began 7/1/2009 during the LDN's first funding cycle. This project is led by Lynda Polgreen, M.D., M.S. Dr. Polgreen is Assistant Professor, David Geffen School of Medicine at UCLA, Pediatric Endocrinology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance, California.

Approximately 85% of individuals with mucopolysaccharidosis (MPS) type I, II, or VI report weekly pain, and 50-60% have significant limitations in their activities of daily living due to MPS-related musculoskeletal disease, despite treatment with hematopoietic cell transplantation (HCT) and/or enzyme replacement therapy (ERT). These patients are often now living into adulthood with good cognitive development, but their quality of life is significantly impacted by their skeletal abnormalities such as kyphosis, scoliosis, and genu valgum; and by progressive joint stiffness, joint contractures, pain, and severe short stature. Unfortunately, there is currently no effective treatment for skeletal disease in MPS. There is a critical need to identify additional therapies to alleviate the burden of MPS musculoskeletal disease in order to improve the health and quality of life of individuals with MPS. Additional therapies might perhaps include, for example, post-HCT supplemental ERT, anti-TNFα drugs, stop codon suppression drugs, or gene therapy. In order to test any innovative therapies, however, musculoskeletal disease progression needs to be quantified, in order to be able to determine efficacy of new therapies.

Until now, the design of therapeutic clinical trials has been limited by the lack of control data on skeletal disease progression and on early biomarkers to predict disease progression. Without these data, impossibly lengthy studies are required to see a significant effect on disease progression. Determination of the progression of skeletal disease *despite treatment* with ERT and/or HCT, along with identifying biomarkers predictive of disease progression, are required to move forward with therapeutic clinical trials in MPS. This is because lengthy, randomized placebo-controlled studies are nearly impossible due to the nature of rare disease research. This unmeetable need for lengthy, randomized placebo-controlled studies has been a significant roadblock to the development of effective new therapeutic agents.

The objective of this study therefore is to quantitatively describe the progression of musculoskeletal disease; and to identify biomarkers that either predict disease severity or could be used as therapeutic targets in individuals with MPS I, II, and VI. It is Dr. Polgreen's hope that the database resulting from this study will strongly facilitate the identification and testing of new therapies for musculoskeletal disease in MPS patients.

In designing this study, Dr. Polgreen hypothesized that skeletal disease in MPS I, II and VI patients will progress over time, and that biomarkers of inflammation, and bone and cartilage turnover, will predict the severity of skeletal disease over time. The specific aims of this study are 1) to characterize the progression of skeletal disease from childhood into young adulthood; and 2) to identify prognostic biomarkers of inflammation, bone remodeling, and cartilage turnover that can predict the progression of skeletal disease and impaired physical function.

To achieve these aims, participants are being evaluated annually with measures of bone health (dual-energy x-ray absorptiometry, peripheral quantitative computed tomography, and hip and spine x-rays); measures of physical function (hand grip dynamometer, range-of-motion testing, and questionnaires focusing on physical function and pain); and laboratory mea-

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Longitudinal study of bone and endocrine disease in children with MPS I, II and VI: A multi-center study of the Lysosomal Disease Network

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surements of biomarkers of bone turnover, cartilage-breakdown, and inflammation. The resulting database of standardized measurements of MPS musculoskeletal disease will allow the field to efficiently move forward with therapeutic clinical trials in patients with MPS.

Dr. Polgreen has established a group of 3 participating centers (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, University of Minnesota, and Children's Hospital and Research Center Oakland) performing standardized evaluations of skeletal health and collecting years of bone and endocrine related data on a cohort of 50 participants with MPS I, II or VI. During the first LDN funding cycle, 55 participants were enrolled in the study. These subjects will continue during this renewed study. Participants who withdraw will be replaced to keep the total cohort at 50 participants. New participants will be recruited from patients treated by physicians within the LDN, from advertisements in the National MPS Society newsletter, the Canadian MPS Society newsletter, the LDN contact registry, and annual gatherings of the MPS Society and lysosomal disease community.

Publications Resulting from LDN Protocol # 6705:

L.E. Polgreen, W. Thomas, E.B. Fung, D. Viskochil, D.A. Stevenson, J. Steinberger, P.J. Orchard, C.B. Whitley, K.E. Ensrud, Low bone mineral content and challenges in interpretation of DXA in children with mucopolysaccharidosis types I, II, and VI. J Clin Densitom 17(1) (2014) 200-206. PMCID: PMC3872499. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/

D.A. Stevenson, K.D. Rudser, A. Kunin-Batson, E.B. Fung, D. Viskochil, E.G. Shapiro, P.J. Orchard, C.B. Whitley, L.E. Polgreen, Biomarkers of bone remodeling in children with mucopolysaccharidosis types I, II, and VI. J Pediatr Rehabil Med 7(2) (2014) 159-165. PMCID: PMC4420175. Article freely available at: http://www.ncbi.nlm.nih.gov-/pmc/articles/PMC4420175/.

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Upcoming Presentation at The American Society of Bone and Mineral Research annual meeting, Oct. 9-12, 2015: L.E. Polgreen, A. Petryk, A. Kelly, L. Scibora, B.S. Miller, C.B. Whitley, E.B. Fung, Early bone deficits measured by pQCT in the mucopolysaccharidoses despite current therapies. Visit: http://www.asbmr.org/annual-meeting

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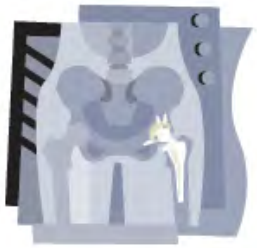
Meet the Principal Investigators



Lynda Polgreen, M.D., M.S.

Lynda Polgreen, M.D., M.S. is a pediatric endocrinologist whose research focuses on skeletal pathology and bone metabolism in the mucopolysaccharidosis diseases (MPS). She is the principal investigator of the Lysosomal Disease Network's multicenter study of biomarkers of skeletal pathology in MPS I, II and VI; the principal investigator on a clinical trial of adalimumab in MPS; and a co-investigator on a clinical trial of enzyme replacement therapy in children with MPS I after hematopoietic cell transplantation.

Lynda Polgreen, M.D., M.S.

Dr. Polgreen's primary contribution to science has been in the area of bone, growth, and endocrine disease in the mucopolysaccharidosis diseases. Her publications have provided evidence of a high prevalence of endocrinopathies (e.g. hypothyroidism, growth hormone deficiency, gonadal failure) in children and adolescents with MPS. In addition, her research team has found that treatment with recombinant human growth hormone (hGH) was variable. For example, children with MPS treated with hGH who had GH deficiency grew much faster than those without GH deficiency, and children with a history of total body irradiation did not respond well to hGH treatment. Dr. Polgreen's research team also documented deficits in bone mineral density in children and adolescents with MPS as compared to healthy controls.

This body of work has changed the clinical care of pediatric patients with MPS I and II by providing evidence for the importance of screening for endocrinopathies; by providing data to use in the decision-making process regarding use of hGH treatment; and by optimizing bone health in children with MPS.

Selected Lynda Polgeeen, M.D., M.S. Publications:

G.P. Forlenza, A. Calhoun, K.B. Beckman, T. Halvorsen, E. Hamdoun, H. Zierhut, K. Sarafoglou, L.E. Polgreen, B.S. Miller, B. Nathan, A. Petryk, Next generation sequencing in endocrine practice. Mol Genet Metab 115(2-3) (2015) 61-71. PMID: 25958132.

A. Petryk, L.E. Polgreen, L. Zhang, J.S. Hodges, D.R. Dengel, P.A. Hoffmeister, J. Steinberger, K.S. Baker, Bone mineral deficits in recipients of hematopoietic cell transplantation: the impact of young age at transplant. Bone Marrow Transplant 49(2) (2014) 258-263. PMCID: PMC3946360. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3946360/.

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National MPS Society Receives 4-Star Charity Rating

For fiscal year 2013, Charity Navigator has awarded the National MPS Society (U.S.) its highest rating — 4 stars — that ranks the Society in the top 25% of charities. This ranking, the most recent available, indicates that the Society outperformed most nonprofits nationwide, and illustrates the highest level of fiscal responsibility and transparency, while staying committed to finding cures and supporting families. In fact, in this review Charity Navigator awarded the Society its maximum possible score of 100 for "Accountability & Transparency."

For details, visit: http://www.charitynavigator.org/index.cfm?bay=search.summary&orgid=8857#.VakwcUUsub5

Hot Off the Press

Selected Recent Publications by Lysosomal Disease Network Investigators

E.G. Shapiro, I. Nestrasil, K.D. Rudser, K. Delaney, V. Kovac, A. Ahmed, B. Yund, P.J. Orchard, J. Eisengart, G.R. Niklason, J. Raiman, E. Mamak, M.J. Cowan, M. Bailey-Olson, P. Harmatz, S.P. Shankar, S. Cagle, N. Ali, R.D. Steiner, J. Wozniak, K.O. Lim, C.B. Whitley, Neurocognition across the spectrum of mucopolysaccharidosis type I: age, severity, and treatment. Mol Genet Metab (2015) Jun 17 pii: S1096-7192(15) 30023-8 [Epub ahead of print]. PMID: 26095521.

M. Aldenhoven, R.F. Wynn, P.J. Orchard, A. O'Meare, P. Veys, A. Fischer, V. Valayannopoulos, B. Neven, A. Rovelli, V.K. Prasad, J. Tolar, H. Allewelt, S.A. Jones, R. Parini, M. Renard, V. Bordon, N.M. Wulffraat, T.J. de Koning, E.G. Shapiro, J. Kurtzberg, J.J. Boelens, Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood 125(13) (2015) 2164-2172. PMID: 25624320.

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F.A. Wijburg, B. Bénichou, D.G. Bichet, L.A. Clarke, G. Kostalova, A. Fainfoim, A. Fellgiebel, C. Forcelini, K. An Haack, R.J. Hopkin, M. Mauer, B. Najafian, C.R. Scott, S.P. Shankar, B.L. Thurberg, C. Tøndel, A. Tylki-Szymanska, U. Ramaswami, Characterization of early disease status in treatment-naive male paediatric patients with Fabry disease enrolled in a randomized clinical trial. PLoS One 10(5) (2015) e0124987, eCollection 2015. PMCID: PMC4425695. Article freely available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124987.

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C.P. Foley, D.G. Rubin, A. Santillan, D. Sondhi, J.P. Dyke, Y.P. Gobin, R.G. Crystal, D.J. Ballon, Intra-arterial delivery of AAV vectors to the mouse brain after mannitol mediated blood brain barrier disruption. J Control Release 196 (2014) 71-78. PMCID: PMC4268109.

Check Your Knowledge of Lysosomal Diseases

How well do you know mucopolysaccharidosis type I?

By Evelyn S. Redtree, M.S.

Introduction to an Understanding of MPS I

The first issue of "**Indications"** (December 2013) presented a brief overview of all the types of mucopolysaccharidosis (MPS) disease. (All past newsletter issues can be downloaded from our homepage. Look in the upper-right area of the page at: www.LysosomalDiseaseNetwork.org.) There, it was explained that the MPS diseases are a group of inherited metabolic diseases caused by the absence or malfunctioning of certain enzymes needed to break down molecules called glycosaminoglycans. These are long chains of sugar carbohydrates in each of the body's cells that help build bone, cartilage, tendons, corneas, skin, and connective tissue. Glycosaminoglycans (formerly called mucopolysaccharides) are also present in the fluid that lubricates joints. People with mucopolysaccharidosis do not produce enough of one of the 11 enzymes required to break down these sugar chains into proteins and simpler molecules. Each deficient enzyme correlates with a specific MPS disease. In healthy individuals, glycosaminoglycans are disassembled into smaller components by the lysosome, a type of cell organelle that functions as a marvelous recycling center, that is present in nearly every type of human cell. After disassembly, the small components are either used to build new, desirable molecules within the cell, or else they are transported away for elimination from the body. When this disassembly and recycling process does not occur normally, glycosaminoglycans accumulate in harmful amounts in the body's cells, blood, and tissues. The result is permanent progressive cellular damage that affects the individual's appearance, physical abilities, organ and system functioning, and in some cases, mental development. Researchers have also identified *secondary cascades* of other pathological intracellular effects that result from this malfunction of the lysosome.[1]

In this issue of "**Indications**," we look in more detail at MPS I. All individuals with MPS I have an absence of, or insufficient levels of, the enzyme α-L-iduronidase, which is essential for disassembling the particular glycosaminoglycans called dermatan sulfate and heparan sulfate.[2] Like most lysosomal diseases, MPS I evidences a continuum of severity. MPS I originally was subdivided into three subtypes: Hurler syndrome (MPS IH), Hurler-Scheie syndrome (MPS IHS), and Scheie syndrome (MPS IS) (representing respectively and in order, decreasing levels of severity). Researchers have not identified biochemical differences between these three subtypes; clinical findings often overlap among them. More recently, therefore, many physicians and researchers have been using the terms "attenuated" (signifying diminished severity) and "severe" MPS I, rather than using those older terms, Hurler, Hurler-Scheie and Scheie.

Severe MPS I / Hurler syndrome, a.k.a. MPS IH

The name Hurler originated with Dr. Gertrude Hurler (1889–1965), a German pediatrician who first published a description of a boy and girl with the condition in 1919. In general, severe MPS I will present within the first year of life, while attenuated forms present later, during childhood.

Clinical Presentation

When learning about clinical presentation it is important to keep in mind the fact that severe MPS I evidences a continuum of severity, and that many individuals with severe MPS I may never experience some of the symptoms described here. For brevity's sake, not all possible signs and symptoms are listed here. For more information, see the "Learn More" links at the end of this article.

Babies with severe MPS I grow normally during most of their first year of life. Growth slows down by the end of the first year, and usually stops by age 3. The final height of most people with severe MPS I is less than 4 feet tall. People with severe MPS I may also appear disproportioned, with their trunks relatively shorter than their legs. Individuals with untreated severe MPS I may have umbilical hernia, inguinal hernia, macrocephaly, hydrocephalus, macroglossia, distinctive syndromic facial features, heart valve abnormalities, or hepato-

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splenomegaly severe enough to interfere with eating and breathing. The clinical features gradually become worse as storage of glycosaminoglycans affects bone, skeletal structure, connective tissues, and organs. The airway may become narrow in some people with MPS I, causing frequent upper respiratory infections and sleep apnea. Heart disease and airway obstruction, both resulting from glycosaminoglycans accumulation, are major causes of death in people with either severe or attenuated MPS I.

People with MPS I often develop corneal clouding, which can cause significant vision problems, especially in dim light. Affected individuals may also have hearing loss and recurrent ear infections. Some individuals with MPS I have joint contractures that affect mobility. Most people with severe MPS I also have progressive dysostosis multiplex involving all bones, which refers to multiple skeletal abnormalities seen on x-ray. Skeletal abnormalities might include some or all of the following: an abnormally shaped skull, curvature of the spine, unstable neck bones, rib shape abnormalities, dislocated hips, joint stiffness, and short, broad hands with bent fingers. Spinal stenosis in the neck may occur, compressing and damaging the spinal cord. Some of these abnormalities may interfere with movement, cause pain or result in significant health problems. Abnormally-shaped teeth are a common finding; they may be widely-spaced and poorly-formed, and their enamel may be fragile. Carpal tunnel syndrome develops in many children with severe MPS I and is characterized by numbness, tingling, pain and weakness in the hand and fingers.

Untreated patients with severe MPS I, now rarely seen in advanced industrialized countries, experience a decline in intellectual function and a more rapidly progressing disease. Their intellectual disability is progressive and profound. Developmental delay is usually present by age one year, and these individuals eventually lose basic functional skills (they undergo developmental regression). Untreated children with severe MPS I usually have a shortened lifespan, often dying by age 10 years. In much of the developed world today, the standard-of-care prevents this progression of disease.

Attenuated MPS I / Hurler-Scheie syndrome, a.k.a. MPS IHS / Scheie syndrome, a.k.a. MPS IS

Scheie syndrome is named after Harold Glendon Scheie (1909–1990), a pioneering American ophthalmologist, a graduate of the University of Minnesota School of Medicine, who identified attenuated MPS I cases by observing corneal clouding. Again, keep in mind that attenuated MPS I evidences a continuum of severity, and that many individuals with attenuated MPS I may never experience some of the symptoms described here. Not all possible symptoms are listed here. For more information, see the "Learn More" links at the end of this article.

The term "attenuated" is used instead of "mild" to describe the less-severely affected MPS I patients because the effects of the disease on a less-severely affected patient are still too significant to be considered *mild*. Individuals at the most-attenuated end of the disease spectrum (historically called Scheie syndrome, or MPS IS) usually grow to a relatively normal height, reaching 5 feet or more. The adult height of individuals whose disease is considered intermediate between severe MPS I and the most-attenuated MPS I (historically called Hurler-Scheie syndrome, or MPS IHS) is variable, but many are below the 5th percentile in height (i.e., shorter than 95% of individuals their age).

Some individuals with attenuated MPS I may have normal or near normal intelligence. Others on the severe end of the spectrum may gradually lose cognitive function. Some individuals may experience some learning difficulties, and some suffer from the cumulative effects of medical problems that hinder their learning and communication. These medical problems may include hearing loss; recurring ear infections; impaired vision possibly from glaucoma, retinal de-

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generation, or clouded corneas; significant pain levels; and the cumulative effects of multiple surgeries. Other attenuated MPS I signs and symptoms may include micrognathia, progressive joint stiffness, carpal tunnel syndrome or other nerve compression, compressed spinal cord, a short neck, aortic valve disease and hydrocephalus.

Shapiro et al. found that the somatic burden of disease for attenuated MPS I individuals was a significant contributor to reduced IQ.[1] The person's age at first treatment for MPS I was also a significant contributor to reduced IQ.[1] Ahmed et al. identified that for attenuated MPS I patients, "a missense mutation L238Q, when paired with a nonsense or other severe mutation, is associated with severe cognitive abnormality and possibly decline starting at a later age than is seen in Hurler syndrome, and with psychiatric problems emerging in adolescence."[3]

Inheritance

All types of MPS I are inherited in an autosomal recessive manner. At this time, the *IDUA* gene (cytogenic location 4p16.3), which codes for the enzyme α-L-iduronidase, is the only gene known whose mutations cause MPS I.

Incidence

Studies conducted independently in multiple countries have mutually confirmed that severe MPS I occurs in approximately 1:100,000 live births. The most-attenuated MPS I is less common, occurring in about 1:500,000 live births. The estimate for individuals whose disease symptoms fall between severe and most-attenuated MPS I is 1:115,000 live births. Although MPS I is individually rare, the incidence of **all MPS diseases combined** is 1:25,000 live births. In comparison, for all lysosomal diseases combined, the estimated incidence is approximately 1:5,000 to 1:7,000 live births. For severe MPS I, about 1:150 people (less than 1%) are carriers of the altered *IDUA* gene.

Treatment of severe MPS I / Hurler syndrome / MPS IH

For children with severe MPS I, the standard of care is hematopoietic cell transplantation (HCT) as early as possible, but definitely before age two years. Currently, only HCT has demonstrated benefit to the brain; however, emerging new treatments may be effective.[1] Emerging new treatments may include intrathecal enzyme administration, substrate reduction drugs, chaperone molecules, and gene therapy.[1] In HCT, the person receives donor cells that carry the normal *IDUA* gene; these donor cells successfully produce the enzyme α-L-iduronidase. The best results are seen when HCT is performed in infancy.

HCT prevents progressive physical and cognitive decline and death.[2] HCT does not completely reverse all the signs and symptoms of severe MPS I. Although HCT halts progression of cognitive decline, many children with severe MPS I continue to show cognitive and physical impairments.[4-7] Shapiro et al. found that HCT prevented hydrocephalus, but not spinal cord compression.[1]

HCT can increase survival, reduce facial stigmata and hepatosplenomegaly, improve hearing, and maintain normal heart function. Due to the morbidity and mortality associated with this transplantation procedure, it is currently recommended primarily for children with severe MPS I, but not for those with attenuated MPS I. Making the decision whether or not to have this procedure performed on their child can be extremely difficult for parents; a few parents choose to forego this treatment because of its high risk of mortality.

Enzyme replacement therapy (ERT) for MPS I is part of the standard-of-care for all MPS I children, whether they have undergone HCT or not.[2,8] (For an overview of the history of enzyme replacement therapy for MPS I, read the December 2014 issue of "**Indications**.") Research by Eisengart et al. (partially funded by the Lysosomal Disease Network) has shown significant cognitive benefit of ERT even when HCT has been success-

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fully performed.[9] They concluded that enzyme replacement therapy in association with HCT enhances cognitive outcomes, and they provided new evidence that ERT is a valuable addition to the standard transplantation protocol.[9] In the U.S., HCT plus ERT is now widely considered by transplanting institutions to be the standard of care for severe MPS I.[8] Peri-HCT ERT is used, providing somatic reduction of glycosaminoglycans accumulation prior to transplantation, as well as post-transplantation.[8]

Treatment of attenuated MPS I / Hurler-Scheie syndrome / Scheie syndrome

As mentioned above, enzyme replacement therapy is the standard-of-care for individuals with attenuated MPS I. ERT delivers laronidase (Aldurazyme®), which is licensed for treatment of the non-central nervous system manifestations of MPS I. (It is unable to cross the blood-brain barrier, unless it is administered intrathecally, which is experimental and in clinical trials currently.) It improves liver size, joint mobility, linear growth, breathing, and sleep apnea in persons with attenuated MPS I. The timing of the initiation of ERT influences the outcome.[1] The earlier treatment is begun, the better effects it will have.

Shapiro et al. found that their "prospective assessment of cognitive function of [attenuated] MPS I patients indicates many unmet needs in this population especially the somatic disease burden and its impact on cognition."[1] They further found that "although most [attenuated] MPS I patients were found to have significant physical problems and some had cognitive problems, they did not receive as much educational or therapeutic support as the MPS IH patients. Very little attention has been paid to the immense educational needs of these attenuated patients. More school interventions and accommodations are warranted."[1]

As noted above, Ahmed et al. had identified a genetic mutation in attenuated MPS I patients called L238Q.[3] Shapiro et al. found that this "L238Q mutation has a significant impact on cognitive ability, suggesting that for this subgroup of MPS I who have a phenotype closer to MPS IH, brain treatment is necessary. Vijay and Wraith report that one patient with [attenuated] MPS I has been transplanted with good results, and Aldhoven suggests that those with a phenotype closer to that of MPS IH could be considered for HCT on an individual basis."[3,6,10]

These findings point to a need to reevaluate the current standard-of-care for attenuated MPS I patients whose phenotype is closer to MPS IH; as well as a need to improve the education and educational support services provided to all attenuated MPS I patients.

Acknowledgement: Some source information for this article was provided by the National Institutes of Health, National Institute of Neurological Disorders and Stroke, and NCATS Office of Communications.

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Learn More . . .

NIH's National Institute of Neurological Disorders and Stroke presents facts about all of the MPS diseases at: http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/detail_mucopolysaccharidoses.htm

The National MPS Society of the U.S.: http://mpssociety.org/

The LDN's Protocol # 6703, "Longitudinal Studies of Brain Structure and Function in MPS Disorders" on the Rare Diseases Clinical Research Network Web site: http://www.rarediseasesnetwork.org/LDN/LDN-6703.htm

and on ClinicalTrials.gov, Search for **NCT01870375** at: https://clinicaltrials.gov/ct2/search/index

Talking Glossary of Genetic Terms: http://www.genome.gov/glossary/

NTSAD Will Soon Issue an RFP for a Research Grant of $40,000

For a second year, the National Tay-Sachs & Allied Diseases Association, Inc. (NTSAD) will make a "Million Dollar Bike Ride" Request for Proposals (RFP). This RFP will be issued in the coming weeks. A grant for $40,000 will subsequently be made to a research project that holds promise for Sandhoff, GM1, Tay-Sachs, Canavan or related genetic diseases. The NTSAD thanks everyone who supported ***Team NTSAD*** on May 9th, 2015; the ***Team NTSAD*** riders; and University of Pennsylvania's Orphan Disease Research Center in making this grant possible! For information, keep watching NTSAD's Web site at: http://www.ntsad.org/.

NTSAD Announces Some 2015 Awarded Research Grants

The NTSAD has announced that it awarded more than $266,000 in grants this spring to five research projects. The grants were made for a one to two-year period, for up to $40,000 per year. These projects represent NTSAD's commitment to fund research that will lead to treatments for rare genetic diseases such as Tay-Sachs, Canavan, GM1 and Sandhoff diseases.

Grants were awarded to the following research proposals:

Development and Validation of a Rapid MS/MS-based Method to Detect HexA deficiency in Tay-Sachs disease
Principal Investigator: Denis Lehotay, PhD
University of Saskatchewan College of Medicine

Intravascular Gene Therapy for Feline GM2
Principal Investigator: Douglas Martin, PhD
Auburn University

Generation of a Knock-in Mutant Hexb Mouse Model
Principal Investigator: Eric R. Sjoberg, PhD
Orphi Therapeutics, Inc.

Late Onset Registry and Repository
Principal Investigator: Florian Eichler, MD
Massachusetts General Hospital

Defining Natural History of Canavan Disease through the Development of an International Registry
Co-funded with The Canavan Foundation
PI: Heather Lau, MD, MS / Co-I: Paola Leone, PhD
New York University

The EveryLife Foundation for Rare Diseases Presents a Rare Disease Scientific Workshop

The EveryLife Foundation for Rare Diseases will present a rare disease scientific workshop entitled "Incorporating the Patient Perspective in Rare Disease Drug Development" on Tuesday, September 15, 2015, 8:00 a.m.–5:00 p.m., at the Willard Hotel in Washington, D.C. For more info, visit: http://everylifefoundation.org/annual-rare-disease-scientific-workshop-7/. For this workshop, the EveryLife Foundation for Rare Diseases is seeking from all stakeholders presentations on the following areas:

- Methodologies or technologies for eliciting the patient perspective
- Industry or patient organization-led disease surveys
- Patient risk benefit analysis on specific drugs
- Examples of quantitative patient input used to influence clinical trial design

To learn about attending or presenting at "Incorporating the Patient Perspective in Rare Disease Drug Development," call (415) 884-0223, or visit: http://everylifefoundation.org/contact-us/.

Recent FDA orphan drug designations:
MediciNova, Inc. for MN-166 (ibudilast) for treatment of **Krabbe disease**

Recent FDA "Breakthrough Therapy" Designations:
Genzyme for olipudase alfa, an enzyme replacement therapy for treatment of non-neurological manifestations of **Niemann-Pick disease type B**

Recent FDA "Fast Track" Designations:
Sanofi and its subsidiary Genzyme for GZ/SAR402671, an oral substrate reduction therapy for the treatment of **Fabry disease**

A committee of the **European Medicines Agency** has recommended granting an EU-wide marketing authorization for sebelipase alfa (Kanuma®, made by Synageva BioPharma Ltd.), for the treatment of **lysosomal acid lipase (LAL) deficiency**, a deadly lysosomal disease. Sebelipase alfa is a recombinant lysosomal human acid lipase, and is the first recombinant product produced from the egg white of transgenic hens (hens whose cells have been modified to include a foreign gene).

Calendar of Upcoming Events

National Niemann-Pick Disease Foundation 23rd Annual Family Support and Medical Conference, August 6 – 9, 2015 in Rosemont, Illinois, USA at Loews Chicago O'Hare Hotel. Details: http://www.nnpdf.org/familyservices_03.html

The Association for Glycogen Storage Disease 37th Annual Patient/Family/Professional Conference, September 18 – 19, 2015 in Oklahoma City, Oklahoma, USA. For updates, visit: http://www.agsdus.org/html/2015conference.html

National Tay Sachs and Allied Diseases Association's **Fifth Annual Day of Hope**, Saturday, September 19, 2015. Since beginning in 2011, $132,457 has been raised on and around the **Annual Day of Hope** with every penny going to funding NTSAD's **Research Initiative**. This year the NTSAD has set the goal of raising $50,000. Their Research Initiative is a comprehensive strategic research program that funds cutting-edge efforts to find a cure and promote scientific collaboration to accelerate these efforts (see page 18). Details: http://www.ntsad.org/index.php/event-listings/day-of-hope

Canadian Organization for Rare Disorders 2015 Annual General Meeting, Tuesday, September 22, 2015, Time: 4:00 p.m. (Eastern Time), Location: **Teleconference**. You must RSVP to: info@raredisorders.ca to receive the teleconference information **before Sept. 21, 2015**.

National Gaucher Conference 2015, October 18 – 19, 2015 at Doubletree Bethesda in Bethesda, Maryland, USA. Hotel special rate deadline: September 17, 2015 (800-445-8667, refer to meeting code NGF). Conference registration deadline: September 28, 2015. Conference will be captured on video and live-streamed online. Afterwards, the conference video in its entirety will be posted on the NGF's website at www.gaucherdisease.org. Details: http://www.gaucherdisease.org/ — then click on "Events."

Acid Maltase Deficiency Association (AMDA) International Patient and Scientific Conference, Oct. 30 - Nov. 1, 2015 in San Antonio, Texas, USA, at the Holiday Inn Riverwalk. Details: http://www.amda-pompe.org/index.php/main/conferences/2015_amda_international_pompe_patient_and_scientific_conference

Imagine & Believe: A Benefit for NTSAD, Thursday, November 5, 2015, Royal Sonesta Hotel, Cambridge, MA. Honoring Robert Coughlin, President and CEO of Massachusetts Biotechnology Council ("MassBio"). Details: http://www.ntsad.org/index.php/event-listings/annual-gala/2015-imagine-believe

The Sanfilippo Foundation Switzerland will hold its 2nd International Conference on "Sanfilippo Syndrome and Related Lysosomal Storage Diseases" at the Starling Hotel & Conference Center in Geneva, Switzerland, November 26th – 28, 2015. Free shuttle service to/from Geneva airport is provided every 15 minutes from 5:10 A.M. to 11:45 P.M. The conference language is English; simultaneous interpretation to French will be provided. For details visit: http://cisml.org/cisml/en/ or contact: corinne.fery@fondation-sanfilippo.ch

12th Annual WORLD*Symposium*, March 1 – 4, 2016 at Manchester Grand Hyatt, San Diego, CA, USA. Preceded by a pre-conference session entitled "Emerging Trends 2016: State of the Art for Experts" on February 29, 2016. Details: http://www.worldsymposia.org/

2016 FSIG Expert Fabry Conference, March 4 – 6, 2016, Wyndham San Diego Bayside, 1355 North Harbor Drive, San Diego, CA, USA. Registration is $75.00 for the first person, then $25.00 for each additional person over age 10 years. Contact FSIG for more information: http://www.fabry.org/FSIG.nsf/Pages2/HomePage

NTSAD's 38th Annual Family Conference will be held April 7 – 10, 2016 in Orlando, Florida at the Rosen Shingle Creek hotel. Watch the NTSAD site for developing details: http://www.ntsad.org/

The International MPS Network's 4th International Symposium on MPS and Related Diseases, in Bonn, Germany. Main meeting: July 14 – 17, 2016. Satellite meeting: July 13 – 14, 2016, entitled "Biology of the Lysosomal Network." For info, visit: www.MPS2016.com. Meeting at Hotel Maritim Bonn (http://www.maritim.com/en/hotels/germany/hotel-bonn/hotel-overview#).

The Association for Glycogen Storage Disease 38th Annual Patient/Family/Professional Conference, September 16 – 17, 2016 in Toronto, Ontario, Canada. For updates, visit: http://www.agsdus.org/

Of Interest . . .

Page 3 of the March 2015 issue of "**Indications**" detailed the long-term goals of the **Leukodystrophy Alliance**. In June 2015 they accomplished a big first step: the first Leukodystrophy Center opened at Children's Hospital of Philadelphia! Details: http://leukodystrophyalliance.org/?p=892

Indications™

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

Keys to Understanding the Lysosomal Disease Network

Lysosomal Disease Network