

# Indications™

Newsletter of The Lysosomal Disease Network™

November 2015

All past issues can be downloaded from the upper-right area of the LDN homepage at: [www.LysosomalDiseaseNetwork.org](http://www.LysosomalDiseaseNetwork.org)

Vol. 2, No. 7

## Batten Disease Support and Research Association (BDSRA) Requests Letters of Intent for 2016 Research Grants

The Batten Disease Support and Research Association (BDSRA) ([www.bdsra.org](http://www.bdsra.org)) has issued a request for letters of intent for the 2016 research grant cycle. BDSRA supports scientific investigations through an annual merit review process, awarding grants to researchers throughout the world. BDSRA seeks innovative research projects that have the potential to advance therapeutic strategies for all or any of the neuronal ceroid lipofuscinoses (more generically known as Batten disease). Each award, depending on funding availability, will be no more than \$60,000 for a one-year period.

Letters of intent must be submitted by **January 4, 2016**. The letters of intent will be reviewed by members of the BDSRA Board and invited scientific reviewers. Requests for full proposals that will be peer-reviewed will be made in February, 2016.

Batten disease has no known treatment or cure. Private funding for Batten disease research has advanced through partnerships of BDSRA with family foundations and European Batten organizations. To submit a letter of intent, applicants need to visit: <https://proposalcentral.altum.com/opportunities.asp?GMID=125>.

## Meet Our Patient Advocacy Groups

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



### The International Advocate for Glycoprotein Storage Diseases

<http://www.ismrd.org/home>

[https://www.facebook.com/ismrdcharity/?fref=ts&ref=br\\_tf](https://www.facebook.com/ismrdcharity/?fref=ts&ref=br_tf)

*By Evelyn Redtree, M.S.*

The International Advocate for Glycoprotein Storage Diseases is an international patient advocacy group that originally had a different name: The International Society for Mannosidosis and Related Diseases (ISM RD). Years after its founding, the mucopolysaccharidoses were included as diseases that ISMRD advocates for, and the name of the group was then changed to "International Advocate for Glycoprotein Storage Dis-

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

## Meet Our Patient Advocacy Groups

### The International Advocate for Glycoprotein Storage Diseases

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eases.” Nevertheless, the acronym ISMRD continues to be used to refer to this group, due to its familiarity, convenience, and the fact that “International Society for Mannosidosis and Related Diseases” is still the officially-registered charitable name for this non-profit organization.

ISMRD is based in Saratoga, California, and aims to be the leading advocate for families worldwide affected by a glycoprotein storage disease. Through partnerships built with medicine, science and industry, it seeks to detect and cure the glycoprotein storage diseases, and to provide a global network of support and information. Its guiding vision is seeking a future in which children with glycoprotein storage diseases can be detected early, treated effectively, and go on to live long, healthy and productive lives.

ISMRD was founded in 1999 in Baltimore, Maryland by Paul and Debora Murphy, parents of a child with  $\alpha$ -mannosidosis, who developed the organization to fill a void that existed for affected families, scientists and physicians. The Murphys were encouraged by a critically-important friendship and cooperative partnership that developed via the early Internet with Dag Malm, M.D., Ph.D., Senior Consultant in Internal Medicine and Gastroenterology at the University of Tromsø Hospital in Tromsø, Norway, a researcher in the Tromsø Mannosidosis Group, and a father of two  $\alpha$ -mannosidosis-affected daughters. Dr. Malm is now a member of ISMRD’s Professional Advisory Board, and continues to be involved in scientific investigations into  $\alpha$ -mannosidosis.

The decision to form ISMRD resulted from a meeting in Baltimore during the autumn of 1998 between Paul Murphy and Dr. Ole K. Greiner-Tollersrud, a professor and researcher in the Department of Medical Biochemistry and Department of Medicine, University Hospital and University of Tromsø, a colleague of Dr. Malm and a member of the Tromsø Manno-

sidosis Group. Discussions about the current pace of research for mannosidosis led to the decision to form a non-profit entity to promote scientific collaborations envisioned by Dr. Greiner-Tollersrud to accelerate understanding of mannosidosis. In the summer of 1999 the ISMRD applied for and was granted advance status as a nonprofit 501 (c) (3) status by the IRS. In 2004 it successfully achieved formal status as a 501 (c) (3) organization upon IRS review of its first five years of existence. Further details about the early days of the ISMRD are available at: [http://www.ismrd.org/about\\_ismrd/how\\_ismrd\\_began](http://www.ismrd.org/about_ismrd/how_ismrd_began).

The diseases that ISMRD is concerned with are:

- $\alpha$ -Mannosidosis
- Aspartylglucosaminuria
- $\beta$ -Mannosidosis
- Fucosidosis
- Galactosialidosis
- Schindler Disease
- Sialidosis, *old nomenclature*: Mucopolipidosis I
- Mucopolipidosis  $\alpha/\beta$ , *old nomenclature*: I-Cell Disease (MLII); Pseudo-Hurler Polydystrophy (ML III)
- Mucopolipidosis III  $\gamma$  [ $\gamma$ ], *old nomenclature*: ML IIIC variant
- Intermediate Mucopolipidosis, *old nomenclature*: Mucopolipidosis II/III. This descriptive term is used in regard to patients who have an intermediate form of ML, between ML alpha and ML beta, who show small stature and skeletal findings similar to individuals with ML  $\alpha$ , but better cognitive function and longer life-span, similar to individuals with ML  $\beta$ .

The nomenclature for mucopolipidosis has been evolving as molecular understanding and clinical experience have improved in the past few decades. Online information sources about mucopolipidosis haven’t necessarily kept current with these recent changes in nomenclature.

ISMRD is governed by a Board of Directors whose backgrounds span nations, diseases and experience. Each Board member serves a two-year term which can be renewed upon approval of the remaining Board members. The Board of Directors is assisted in the execution of its mission and goals by a distinguished Professional Advisory Board who are members of the international scientific and medical community. To see



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## Meet Our Patient Advocacy Groups

### The International Advocate for Glycoprotein Storage Diseases

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As of July 2015 the new ISMRD President is Jackie James, mother of 20-year-old Anna, who has ML  $\alpha/\beta$ . Jackie said, "My goal for the next couple of years is to raise more awareness of the handful of rare diseases that ISMRD covers, through social media, other media coverage, friends, family, and the medical community. Research is a priority, and we plan on focusing on fund-raising for specific research projects, as well as working with other lysosomal/glycoprotein storage disease advocate organizations in joint fundraising efforts. One of the specific research areas we are targeting is treatment for bone disease in mucopolipidosis. Researchers who wish to propose projects in this area, or in other research areas of our covered diseases, should definitely contact us at our e-mail address" (info@ismrd.org).



Anna (left) and Jackie James

When asked about her personal background, Jackie responded, "I am originally from the UK but moved to St. Louis many years ago, where I live with my husband and two children. I own and operate a British tea room in Saint Louis. I am a certified tea specialist with the world tea academy and am now working toward becoming a certified WTA tea sommelier. I have been an ISMRD Board Member for the past four years, and ISMRD is very close to my heart.

I am so excited and honored to be named ISMRD's new President!"

The activities of ISMRD include holding recurring scientific/family conferences. Their first conference convened in 2004 in Washington D.C. These conferences have continued to be convened every 3-5 years. In July 2015, the conference entitled "Glycoproteinoses: Fourth International Conference on Advances in



Pathogenesis and Therapy" was hosted by ISMRD in St. Louis, in conjunction with the Washington University in St. Louis School of Medicine. Carolyn Paisley-Dew, ISMRD Board Member and editor of their newsletter said, "The 4<sup>th</sup> International Conference hosted by ISMRD was the biggest conference ever! More than 200 people attended. Almost all of our nine disorders were represented by an affected family. Speakers gave presentations on all of our disorders. People came from 15 countries and 4 continents!" For an in-depth review of this meeting, read the ISMRD Sept. 2015 newsletter, that can be downloaded by visiting: [http://www.ismrd.org/news\\_and\\_events/newsletter](http://www.ismrd.org/news_and_events/newsletter). They plan to host their next international scientific/family conference in 2 or 3 years.



*Emma and John O'Connor, July 2015 meeting attendees from Ireland, talking with Dr Jules Leroy. Dr. Leroy is former Professor and Chairman of Pediatrics at Ghent University of Medicine in Belgium. Dr. Leroy provides expertise on metabolic disorders and intellectual disabilities. Dr. Leroy discovered the lysosomal disease mucopolipidosis II. He collaborates with Dr. Sara Cathey in further delineating the clinical, biochemical and molecular manifestations of mucopolipidosis II and related conditions.*

*covered the lysosomal disease mucopolipidosis II. He collaborates with Dr. Sara Cathey in further delineating the clinical, biochemical and molecular manifestations of mucopolipidosis II and related conditions.*



*Child attendees at the July 2015 meeting included Sergio Cardenas (right), Aoihe O'Connor (in striped dress), and Zachie Hagggett (left of Aoihe).*

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## Meet Our Patient Advocacy Groups

### The International Advocate for Glycoprotein Storage Diseases

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ISMRD also provides practical support for families who are newly-diagnosed, by connecting them confidentially with other affected families. Another ISMRD service is their “sunshine committee” that provides caring outreach and emotional support to families with children in hospital, or who have had a bereavement.



ISMRD Board of Directors at the July 2015 meeting. Back row, left: Jenny Noble, Vice President/Admin, New Zealand; Jackie James, President, USA; Susan Kester, Board member, USA; Tish Adkins, Board member, USA; Carolyn Paisley-Dew, Board member, Australia. Front row, left: John Forman, Vice President Research, New Zealand; Dr. Sara Cathey, USA (not a Board Member); Mark Stark, Treasurer, USA.

Jackie said, “ISMRD struggles to raise funds because we are an international organization, which disqualifies us from many grants. Funds that support our research are raised by families. We are seriously seeking to work with other similar lysosomal storage disease organizations, to maximize funding.” Jackie encourages other lysosomal disease organizations possibly interested in joint fund-raising to contact ISMRD. She continued, “Our scientific/family conferences receive some extremely valuable and generous support from some pharmaceutical companies, foundations, universities, and individuals.” For exam-



ple, their July 2015 meeting was supported by Washington University in St. Louis, Amicus, Genzyme, Shire, Ultragenyx, PTS Therapeutics, Zymenex, and several foundations and individuals. Their September 2015 newsletter provides funding details on page 12 at: [http://www.ismrd.org/news\\_and\\_events/newsletter](http://www.ismrd.org/news_and_events/newsletter).

### Research Support: An ISMRD Priority

In 2006 ISMRD partnered with the Greenwood Genetic Center, headquartered in South Carolina (<http://www.ggc.org/>), to develop a natural history study for the diseases for which ISMRD advocates. That natural history study continues to this day, led by Dr. Sara Cathey at the Greenwood Genetic Center offices in North Charleston, SC. The study expanded to include Australian and New Zealand patients. Most recently, Dr. Cathey collected biological samples at the July gathering in St. Louis from attendees with glycoproteinosis diseases. This study is recruiting patients; detailed information is available on ClinicalTrials.gov. Search for # NCT 01891422.

As reported in the October 2015 issue of “Indications,” the National MPS Society of the U.S. and ISMRD have partnered to fund an ML II/III grant. The grant was awarded to Dr. Heather Flanagan-Steet at the Complex Carbohydrate Research Center at the University of Georgia. The grant is \$20,000 for each of two consecutive years. Dr. Flanagan-Street’s project is entitled “Investigating the role of cathepsin proteases in ML-II cardiac pathology.” For details, visit: [http://www.ismrd.org/news\\_and\\_events](http://www.ismrd.org/news_and_events).

These research activities emphasize the fact, often noted in these pages, that a group’s small size need not be an impediment to accomplishing ambitious research goals!



Tyler Hawnault, Dr. Alessandra d’Azzo and Amanda Gertner enjoying each other at the July 2015 meeting in St. Louis.

## LDN Research Matters



### Magnetic Resonance Spectroscopy (MRS) to Determine Neuroinflammation and Oxidative Stress in MPS I

By Evelyn S. Redtree, M.S. and Igor Nestrasil, M.D., Ph.D.

LDN Pilot Project 2, entitled “Magnetic resonance spectroscopy (MRS) to determine neuroinflammation and oxidative stress in MPS I,” is led by Igor Nestrasil, M.D., Ph.D. at the University of Minnesota in Minneapolis. For this study, Dr. Nestrasil hypothesizes that neurochemical profiles will differ between MPS IH (Hurler syndrome) post-hematopoietic cell transplantation (HCT) patients, MPS IHS (Hurler-Scheie syndrome) patients undergoing regularly recurring enzyme replacement therapy (ERT), and age-matched controls. Additionally he hypothesizes that inflammation and oxidative stress will be more pronounced in ERT patients than in post-HCT patients. He also hypothesizes that within the Hurler-Scheie syndrome patient group, which is highly clinically diverse, there will be a higher degree of neuroinflammation and oxidative stress in the severely-affected patients (as defined by their genotype and clinical status), compared to the less-severely affected patients.

#### Background

ERT is administered to treat attenuated forms of MPS I, including Hurler-Scheie syndrome (the intermediate form) and Scheie syndrome (the “mild” form). Since enzymes used in intravenous ERT do not pass the blood-brain barrier, intravenous ERT is currently thought to be only effective for treating non-neurological symptoms. This may also explain the neurological symptoms present in intravenous ERT-treated Hurler-Scheie and Scheie syndrome patients.

In Hurler-Scheie syndrome, the clinical presentation is highly variable and can include cognitive, attention, and behavioral deficits with slow decline over time. Some Hurler-Scheie syndrome patients develop a severe neurological phenotype later in life.



Recent data from the LDN study “Longitudinal studies of brain structure and function in MPS disorders” indicates that a “severely-affected” genotype (L238Q) is associated with this gradual cognitive decline, including psychiatric symptoms.<sup>1</sup> The underlying pathogenic mechanism for such clinical variability and slow decline is not yet well understood. The role of neuroinflammation and oxidative stress is one avenue of investigation that may clarify this variability. Identifying biomarkers that accurately describe the underlying and ongoing brain pathology is key in understanding the disease, and investigating the possibility of developing new therapeutic approaches for MPS I patients.

In various neurodegenerative disorders such as Alzheimer’s disease, neuroinflammation and oxidative stress represent the main cause of disease progression.<sup>2,3</sup> Are neuroinflammation and oxidative stress contributing to the worsening in MPS I, and particularly in the Hurler-Scheie syndrome subgroup? If they are contributing, should the Hurler-Scheie syndrome patients undergo HCT as early in life as the Hurler syndrome patients? Would MPS I patients benefit from central nervous system (CNS)-targeted antioxidative or anti-inflammatory treatments? To seek answers to these crucial questions, this Pilot Project employs brain MR spectroscopy to obtain neurochemical profiles, and cerebrospinal fluid and blood analyses to identify reliable biomarkers of inflammation and oxidative stress that may point to ongoing brain pathology.

#### Methods

Research subjects over the age of 12 years will be recruited for this study. Half of the subjects will be post-HCT Hurler syndrome patients, and half will be Hurler-Scheie or Scheie syndrome patients receiving ERT. MR spectroscopy will be used to image 10 post-HCT Hurler syndrome patients and 10 Hurler-Scheie or Scheie syndrome patients receiving ERT, including 4-5 patients with the L238Q genotype, which is associated with a more severely-affected Hurler-Scheie phenotype<sup>1</sup>. Ten normal, healthy controls will also be imaged with MR spectroscopy.

In addition to employing spinal taps and blood draws in an attempt to identify reliable biomarkers, methods developed in the LDN’s MPS longitudinal study to measure disease severity will be used in this study.

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## LDN Research Matters



### Magnetic Resonance Spectroscopy (MRS) to Determine Neuroinflammation and Oxidative Stress in MPS I

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These methods include neuropsychological tests and the recently-developed MPS-specific Physical Symptom Score.<sup>4</sup>

This Pilot Project will use all of these approaches to better understand the CNS pathological changes in MPS diseases, and to identify biomarkers of underlying pathology that may play a key role in quantifying treatment outcomes.

#### References Cited:

<sup>1</sup>A. Ahmed, C.B. Whitley, R. Cooksley, K.D. Rudser, S. Cagle, N. Ali, K. Delaney, B. Yund, E.G. Shapiro, Neurocognitive and neuropsychiatric phenotypes associated with the mutation L238Q of the  $\alpha$ -L-iduronidase gene in Hurler-Scheie syndrome. *Mol Genet Metab* 111(2) (2014) 123-127. PMID: PMC3939822. Article freely available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3939822/>.

<sup>2</sup>A. Arfi, M. Richard, C. Gandolphe, D. Bonnefont-Rousselot, P. Therond, D. Scherman, Neuroinflammation and oxidative stress phenomena in MPS IIIA mouse model: the positive effect of long-term aspirin treatment. *Mol Genet Metab* 103(1) (2011) 18-25. PMID: 21353610.

<sup>3</sup>P. Agostinho, R.A. Cunha, C. Oliveira, Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. *Curr Pharm Des* 16(25) (2010) 2766-2778. PMID: 20698820.

<sup>4</sup>A. Ahmed, K.D. Rudser, A. Kunin-Batson, K. Delaney, C.B. Whitley, E.G. Shapiro, Mucopolysaccharidosis (MPS) Physical Symptom Score: development, reliability, and validity. *JIMD Rep* 2015 Aug 25. [Epub ahead of print]. PMID: 26303610.



## EveryLife Foundation's Rare Artist Contest is Accepting Entries Through December 15th

The 2015 Rare Artist contest is in its final month, and EveryLife Foundation is seeking submissions of photos of art that has been created in any of these media: painting, photography, mixed media, collages, pottery, and sculptures. The contest is easy to enter on the Rare Artist Facebook page (go to: <http://www.rareartist.org/2015-art-contest/>). Entry deadline is December 15th, and popular voting is open (on the Facebook page) through December 22nd, 2015.

Entrants are allowed to submit one piece in the contest for their age group. Two awards will be given in each category (one decided by popular vote, and one decided by a panel of rare disease community leaders):

Children (aged 4-11 years): \$100 gift card

Teens (aged 12-17 years): \$250 gift card

Adults (aged 18+ years): \$500 gift card

Adults - Photography/Digital Art (aged 18+ years): \$500 gift card

Winning pieces will be displayed in Washington D.C. at EveryLife Foundation's Rare Artist Reception on March 3, 2016. If you have questions or concerns about the contest, please email Grant Kerber at: [gkerber@everylifefoundation.org](mailto:gkerber@everylifefoundation.org), after visiting the URL listed above.

## Did You Know?

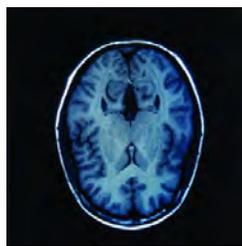


### Travel Scholarship is Available

The EveryLife Foundation for Rare Diseases provides travel stipends for *patient advocates* in United States (outside of the D.C. metro area) to attend FDA meetings & Capitol Hill events. Scholarships are given to ensure patients have the ability to participate in these important meetings. Travel stipends range from \$300-\$1,000 maximum. They are intended to help offset travel costs, but not to cover all costs in full. The amount of the award depends upon the distance the recipient has to travel for the event.

Learn More: <http://everylifefoundation.org/travel-scholarship-application/>

## Meet the Principal Investigators



### Igor Nestrasil, M.D., Ph.D.

Igor Nestrasil, M.D., Ph.D., Research Assistant Professor of Pediatrics at the University of Minnesota and LDN Neuroimaging Core Director, is also co-investigator of the ground-breaking LDN study “Longitudinal studies of brain structure and function in MPS disorders.” He is also the principal investigator of LDN Pilot Project I, “Magnetic resonance spectroscopy (MRS) to determine neuroinflammation and oxidative stress in MPS I.”



Igor Nestrasil, M.D., Ph.D.  
Director, LDN Neuroimaging Core

Dr. Nestrasil, a native of the Czech Republic, was awarded a Proshak-Fulbright Scholarship in Medical Sciences and started his research at the University of Minnesota in 2007. Dr. Nestrasil’s studies include multi-modal brain magnetic resonance imaging (MRI) and analyses, including automated, semi-automated,

manual, volumetric and diffusion tensor imaging (DTI) techniques, resting-state functional MRI, and MR spectroscopy in humans and animal models.

Within the Lysosomal Disease Network, Dr. Nestrasil has created and successfully implemented neuroimaging protocols that are used across multiple LDN research sites, as well as in clinical trials funded by both federal funds and pharmaceutical companies. Dr. Nestrasil said, “One of the challenges to LDN research in multicenter studies is the reliability of captured images across centers. Achieving reliability depends on the scanner type and the sequences that are employed. To increase reliability for data pooling, we



insist on adoption of uniform sequences, imaging of a normal control and sending it to our center for a quality assessment to determine acceptability and compatibility, and subsequent central analysis of all scans at the University of Minnesota.” At the University of Minnesota, Dr. Nestrasil supervises imaging data processing and analysis. He collaborates with University of Minnesota researchers at the Center for Magnetic Resonance Research (CMRR), a state-of-the-art and world-leading facility in MRI research, and the Minnesota Supercomputing Institute (MSI), which provides Dr. Nestrasil’s research activities with advanced computing infrastructure.

### Selected Igor Nestrasil, M.D., Ph.D. Publications:

J.M. Provenzale, I. Nestrasil, S. Chen, S.H. Kan, S.Q. Le, J.K. Jens, E.M. Snella, K.N. Vondrak, J.K. Yee, C.H. Vite, D. Elashoff, L. Duan, R.Y. Wang, N.M. Ellinwood, M.A. Guzman, E.G. Shapiro, P.I. Dickson, Diffusion tensor imaging and myelin composition analysis reveal abnormal myelination in corpus callosum of canine mucopolysaccharidosis I. *Exp Neurol* 273 (2015) 1-10. [Epub ahead of print]. PMID: 26222335.

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.

E.G. Shapiro, I. Nestrasil, A. Ahmed, A. Wey, K.D. Rudser, K.A. Delaney, R.K. Rumsey, P.A. Haslett, C.B. Whitley, M. Potegal, Quantifying behaviors of children with Sanfilippo syndrome: the Sanfilippo Behavior Rating Scale. *Mol Genet Metab* 114(4) (2015) 594-598. PMID: PMC4390542.

B. Yund, K.D. Rudser, A. Ahmed, V. Kovac, I. Nestrasil, J. Raiman, E. Mamak, P. Harmatz, R. Steiner, H. Lau, P. Vekaria, J.R. Wozniak, K.O. Lim, K. Delaney, C.B. Whitley, E.G. Shapiro, Cognitive, medical, and neuroimaging characteristics of attenuated mucopolysaccharidosis type II. *Mol Genet Metab* 114(2) (2015) 170-177. PMID: PMC4312717.

R. Schiffmann, J. Mayfield, C. Swift, I. Nestrasil, Quantitative neuroimaging in mucopolysaccharidosis type IV. *Mol Genet Metab* 111(2) (2014) 147-151. PMID: PMC4097300.

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

## Check Your Knowledge of Lysosomal Diseases

### How well do you know mucopolysaccharidosis type II?

By Evelyn S. Redtree, M.S.



In the May and August 2015 issues of “**Indications**” we took an in-depth look at MPS III and MPS I, respectively. In this issue we are exploring MPS II, also called Hunter syndrome or Hunter disease. The name Hunter syndrome arose in 1917, when Dr. Charles Hunter, a professor of medicine in Manitoba, Canada, first described two affected siblings with MPS II.

#### MPS II Inheritance

MPS II is a recessive X-linked lysosomal disease in which the mother, who is a carrier for the disease, passes one defective *IDS* gene to a son, via her affected X chromosome. The *IDS* gene is at cytogenic location Xq28. Although very rare, it is also possible for a spontaneous mutation in the *IDS* gene to have occurred in an individual, which would be indicated by their mother not being a carrier of any defective *IDS* gene. Except in extremely rare cases



affecting carrier females, only males will be affected by Hunter syndrome.<sup>1</sup> When females are affected, some studies have suggested that the female’s normal X chromosome is preferentially inactivated.<sup>2</sup> Maternal female relatives and sisters of boys with MPS II may be carriers of the *IDS* gene mutation(s). If the specific genetic mutation(s) of boys with MPS II have been identified, DNA testing can then determine the carrier status of sisters and maternal female relatives. Female carriers have a 50% chance of each of their male children having MPS II, and a 50% chance of each of their female children being a carrier. It is very important, therefore, that each female relative undergo genetic counseling and, if possible, genetic analysis to determine if they are a carrier, so that their reproductive options are better informed.

#### MPS II Incidence

The National MPS Society of the U.S. estimates that the incidence is 1:100,000 to 1:150,000 male births. The MPS Society of the UK estimates that the incidence of MPS II is 1:100,000 male births. Scarpa et al. estimated that European incidence is between 1:140,000 and 1:156,000 live births.<sup>3</sup>

#### MPS II Pathological Mechanism

MPS II results from absent or insufficient iduronate-2-sulfatase (I2S) enzyme, which is coded by the *IDS* gene. I2S is necessary for the metabolism of heparan sulfate and dermatan sulfate. Without successful and adequate metabolism of heparan sulfate and dermatan sulfate, glycosaminoglycans (formerly called mucopolysaccharides) accumulate in all cells of the body.

Hundreds of different pathogenic mutations in the *IDS* gene have been identified, including point mutations, small deletions and insertions, missense and nonsense mutations, splice site mutations, and intragenic deletion of exons, which all result in iduronate-2-sulfatase deficiency.<sup>4,5</sup> MPS II presents as a severe form (absent enzyme) or an attenuated form (insufficient enzyme). As in many other MPS diseases, there exists a large continuum among the phenotypes of MPS II, which can be found even among members of the same immediate family. Persons with the attenuated form also demonstrate great variability in their age of onset, age of diagnosis, somatic disease burden, and rate of disease progression.<sup>6</sup> Approximately 20% of persons with MPS II have gene mutation(s) that result in complete absence of the I2S enzyme, a finding that suggests severe disease.<sup>4</sup> In comparison, attenuated-form phenotypes cannot be precisely predicted by their genotype or any currently-known bio-

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## Check Your Knowledge of Lysosomal Diseases

### How well do you know mucopolysaccharidosis type II?

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markers.<sup>6</sup> Even in persons who have the same small amount of I2S enzyme activity, and even within the same family, there can be variations in severity of disease that cannot be explained by the I2S enzyme level or specific gene mutation.<sup>4</sup> Clearly, researchers working in the human genome have their work cut out for them!

#### Clinical Presentation of MPS II

The signs and symptoms of MPS II are not apparent at birth, but gradually become evident as the cellular accumulation of glycosaminoglycans (GAG) increases. In severe MPS II, onset occurs between 2-4 years of age (usually prior to age 3 years), with death often occurring before age 15 years. In attenuated forms the age of onset is highly variable. Persons with attenuated MPS II may survive well into their adult years. They may have a reasonably normal life span if their physical problems, such as heart disease, are not severe.<sup>1</sup> In terms of prognosis, at this time the differentiation of those who will develop severe MPS II from those who will develop the attenuated form is problematic.<sup>7</sup>

Eventually, persons with the severe form of MPS II demonstrate cognitive and behavioral disturbances. Behavioral disturbances include severe hyperactivity and emotional lability.<sup>7</sup> While young, persons with severe MPS II may be strong and difficult to supervise.<sup>4</sup> They have an increased tolerance of pain—bumps and bruises or ear infections that would be painful for other children often go unnoticed in persons with severe MPS II.<sup>4</sup> Toilet training may be achieved briefly by some, but most will remain in diapers.<sup>4</sup> In contrast, persons with attenuated MPS II may appear normal in behavior.<sup>4</sup>

Individuals with the severe form of MPS II have progressive neurodegeneration and mental impairment that progresses to profound mental retardation, and severe and progressive somatic (physical) problems.<sup>4</sup> In the groundbreaking LDN-funded longitudinal study “Longitudinal Studies of Brain Structure and Function in MPS Disorders,” Dr. Elsa Shapiro and her research team found that individuals with attenuated MPS II demonstrated no severe psychopathology.<sup>7</sup> Rather, significant concerns about social withdrawal, attention span, processing of information and interpersonal problems did arise.<sup>7</sup> Dr. Shapiro and colleagues found that sometimes the cognitive decline and emotional problems found in severe MPS II have a later onset, so it is difficult to determine early whether a patient had attenuated disease or not.<sup>7</sup>

Also for attenuated MPS II, the burden of somatic disease was found to be similar to the somatic disease burden of attenuated MPS I patients.<sup>7</sup> In individuals with attenuated MPS II Shapiro et al. found poor quality of life in the physical health domain, but not in the psychological health domain (unpublished data).<sup>7</sup> Persons with attenuated MPS II may have the same somatic signs and symptoms as those seen in individuals with severe MPS II, but with later onset and slower progression.<sup>4,7</sup> Always keep in mind the key concept: a large continuum exists among the phenotypes of MPS II.



Tanjuakio et al. studied 74 Japanese Hunter syndrome patients.<sup>8</sup> They found that excessive growth occurred at an early age in many of these patients.<sup>8</sup> “Birth weights and lengths of patients were near normal, but by aged 1.5 and 3 years, 30% and 15%, respectively, had both weight and height above the 97<sup>th</sup> percentile, confirming excessive growth in Hunter syndrome patients.<sup>8</sup> More than 50% of patients had weights above the 97<sup>th</sup> percentile of the normal population at both ages.”<sup>8</sup>

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## Check Your Knowledge of Lysosomal Diseases

### How well do you know mucopolysaccharidosis type II?



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Keeping in mind that not all of the following are likely to be found in any single individual, the somatic signs and symptoms of MPS II may include: dysostosis multiplex, kyphosis, cervical spinal cord compression, shortened stature, short neck, short, broad hands with stubby fingers, short trunk length compared to the extremities, carpal tunnel syndrome and/or other nerve entrapments or compression, scaphocephaly, macrocephaly, flattened bridge of nose, enlargement of tonsils and adenoids, obstructive sleep apnea leading to inadequate oxygen levels and chronic sleep deprivation, tracheal malacia, macroglossia, thick lips, broad gum ridges, poorly-formed widely-spaced teeth with fragile enamel, hypertrichosis, chronic middle ear and sinus infections, chronic upper respiratory infections, abnormal retinal pigmentation and papilledema, poor peripheral vision, progressive hearing impairment (conductive and/or sensorineural), progressing joint stiffness, communicating hydrocephalus, hepatosplenomegaly, inguinal hernia, umbilical hernia, cardiomyopathy, endocardiofibroelastosis, progressive valvular heart disease, coronary artery disease, extensive Mongolian spots, pebbly ivory-colored skin lesions on back, upper arms, shoulders and thighs, and intractable diarrhea. This is not a comprehensive list. For more information, the National MPS Society (U.S.) and the MPS Society (U.K.) offer superb downloadable .pdf guides to MPS II. Visit: <http://mpssociety.org/education/mps-and-ml-booklets/> and <http://mpssociety.org.uk/conditions/mps-diseases/mps-2/>.

The progressive hearing impairment (conductive and/or sensorineural) mentioned above is so widespread as to be nearly universal among the MPS II population.<sup>7</sup> This impairment causes major obstacles to successful life adjustment for many, and creates significant disability for some.<sup>7</sup> The communicating hydrocephalus mentioned above is also a major problem for persons with MPS II, because they can have fairly abrupt onset of hydrocephalus, with its serious sequelae.<sup>7</sup> Monitoring of intra-cranial pressure involves either sophisticated brain imaging or lumbar puncture. Since general anesthesia would be needed for these procedures in this population (at least during childhood), the cumulative impact of this ongoing monitoring of intra-cranial pressure on the patients' somatic burden of disease is substantial.

In the longitudinal study “Longitudinal Studies of Brain Structure and Function in MPS Disorders,” Elsa Shapiro and her research team also found that the MRI brain scans of attenuated MPS II patients are often very abnormal, but this abnormality (which may include cysts, or Virchow–Robin spaces<sup>9</sup>) did not correlate with cognitive ability.<sup>7</sup>

In the same study, Yund et al. made the first systematic analysis of attenuated MPS II phenotypes.<sup>6</sup> Their significant results included these findings:

- MPS II attenuated patients have normal IQ, memory, and executive function.<sup>6</sup>
- MPS II attenuated patients under 25 years of age show decreased attention span relative to population norms and controls.<sup>6</sup> Measures of attention were one standard deviation below the average range.<sup>6</sup>
- The corpus callosum volume of MPS II attenuated patients under 25 years of age is decreased compared to age-matched controls.<sup>6</sup> Corpus callosum volumes were 22% different from controls, a significant amount.<sup>6</sup>
- MPS II attenuated patients have less age-related brain white matter volume increases than controls.<sup>6</sup>
- Somatic disease burden and white matter and corpus callosum volumes were significantly associated with attention deficits in MPS II attenuated patients.<sup>6</sup>

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## Check Your Knowledge of Lysosomal Diseases

### How well do you know mucopolysaccharidosis type II?



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The authors concluded that “despite treatment with enzyme replacement therapy (ERT), physical symptoms exact a heavy toll on attention [in MPS II attenuated patients], which presumes an inability to process information efficiently and to fatigue easily. Inefficient processing of visual information which is the consequence of poor ability to manage attention can lead to lack of success academically and in the real world. Awareness by the patient and caregivers with appropriate management and symptomatic support will benefit the attenuated MPS II patient.”<sup>6</sup>

#### Treatment of MPS II

Early diagnosis of MPS II is *critical* because the earlier MPS II is diagnosed, the sooner potential treatment options can be explored and supportive care begun.<sup>4</sup> This may prevent some of the irreversible damage.<sup>4</sup> Including MPS II in newborn screening panels is one way to achieve this early diagnosis. At this time, few states include MPS II in newborn screening. To learn about your state’s list of newborn-screened disorders, visit: <http://www.babysfirsttest.org/>.

The current standard-of-care treatment for MPS II is enzyme replacement therapy (ERT) to reduce GAG accumulation.<sup>10,11</sup> ERT as a treatment for MPS II is more effective in preventing somatic signs and symptoms when it is initiated very early in life—this is why including MPS II in newborn screening is so important.

On July 24, 2006, the FDA granted marketing approval for Elaprase® (idursulfase) use in the treatment for MPS II. Elaprase® is a long-term ERT for patients with a confirmed diagnosis of MPS II, which has also been approved for use in the European Union. Elaprase® was developed and is produced by Shire, and is given as weekly intravenous infusions to replace the missing enzyme. It improves lung function, endurance, reduces the size of the liver, and decreases GAG levels in urine. It does not cross the blood-brain barrier at normal intravenous doses, and thus is not anticipated to have an impact on any neurocognitive decline occurring in individuals with MPS II. For more information on the treatment, visit <http://www.elaprase.com/>.

#### Ongoing Current Research

Shire’s ongoing study entitled “AIM-IT” is a controlled, randomized, two-arm, open-label, assessor-blinded study of intrathecally-administered idursulfase-IT, whose formulation differs from that of the intravenous formulation, administered in conjunction with intravenous Elaprase® ERT, in male pediatric patients who have Hunter syndrome and early cognitive impairment. AIM-IT is an international multicenter study designed to determine whether the investigational therapy – idursulfase-IT – may be effective in slowing the progression of cognitive impairment in pediatric patients currently receiving intravenous Elaprase® (idursulfase) ERT. The estimated primary completion date of this study is February 2016. Search for: NCT02055118 on ClinicalTrials.gov; or visit: <http://www.shiretrials.com/en/studies/clinicaltrials/en/2014/02/05/16/06/hgt-hit-094>. Patients who have completed AIM-IT are eligible to be enrolled in an extension study of idursulfase-IT, designed to collect long-term safety data. For details about the extension study, search for NCT01506141 at ClinicalTrials.gov.

Shire’s Web site has a page summarizing its numerous clinical trials in the MPS diseases: <http://www.shiretrials.com/en/studies>.

ArmaGen has a Phase I open-label, adult-male-patient, safety and dose-finding clinical trial underway for its therapeutic agent AGT-182 in MPS II. AGT-182 is a molecular “Trojan horse” fusion protein of iduronate-2-sulfatase

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## Check Your Knowledge of Lysosomal Diseases

### How well do you know mucopolysaccharidosis type II?



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engineered to cross the blood-brain barrier by binding to insulin receptors located in the cell membrane of specific cells of the brain's capillaries.<sup>12</sup> This study is recruiting subjects. Search for NCT02262338 on ClinicalTrials.gov to learn the details, including the list of participating sites.

ReGenX Biosciences is developing RGX-121 for MPS II, which involves a one-time delivery of a normal copy of the gene encoding I2S enzyme to cells of the central nervous system, allowing the body to produce enough enzyme to ameliorate symptoms without the need for repetitive treatment. For more information visit <http://www.regenxbio.com/>.

Sangamo BioSciences is developing a gene therapy approach to lysosomal disorders, beginning with MPS I and MPS II. Sangamo's genome-editing approach is designed to provide life-long production of sufficient quantities of corrective enzyme from the patient's own liver to eliminate the need for chronic enzyme replacement therapy. They are currently in the pre-clinical phase with this work; for more information visit: <http://www.sangamo.com/pipeline/llds.html>.

This is an extremely promising time in history in regard to treatment or cure for MPS II. The National MPS Society's page detailing clinical trials can keep you posted on emerging developments: <http://mpssociety.org/clinical-trials/>.

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### How well do you know mucopolysaccharidosis type II?



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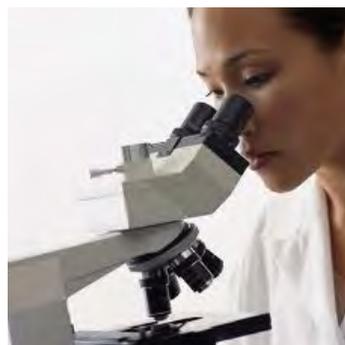
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## Action Alert from the EveryLife Foundation: Please Ask Your Senators to Co-Sponsor the OPEN ACT to Repurpose Drugs for Rare Disease Patients

The “Orphan Product Extensions Now, Accelerating Cures & Treatments” bill, a.k.a the **OPEN ACT** (House of Representatives # 971/Senate # 1421), could bring hundreds of safe, effective, and affordable medicines to rare disease patients within the next several years by incentivizing drug makers to repurpose therapies for the treatment of life-threatening rare diseases and pediatric cancers. EveryLife Foundation, NORD, Global Genes, Genetic Alliance and an additional 155 patient organizations support this bipartisan legislation.



The OPEN ACT provides this incentive to pharmaceutical companies by making available an additional six months of market exclusivity for the repurposed treatment, as long as the sponsor company establishes that the therapy is designated to treat a rare disease, and obtains a rare disease indication from the Food and Drug Administration on the drug label. This would apply to currently-approved drugs that are still under patent. The six-month extension would be in addition to other types of exclusivity, such as pediatric or qualified infectious disease product exclusivity.

The following Web page has a link to an easy-to-use online tool for writing to your Senators, greatly reducing the time required: <http://www.congressweb.com/KAKI/38>



## Calendar of Upcoming Events



The Sanfilippo Foundation Switzerland will hold its 2<sup>nd</sup> 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](mailto:corinne.fery@fondation-sanfilippo.ch)

2016 Rare Disease Week on Capitol Hill, schedule presented by Rare Disease Legislative Advocates: February 29th: Rare Disease Day at the NIH; and rare disease documentary screening & cocktail reception. March 1st: Legislative conference at FHI 360. March 2nd: Lobby Day Breakfast & hill meetings. March 3rd: Congressional Caucus briefing; and Rare Artist reception. For details: <http://rareadvocates.org/rdw/> or call their office in Washington, D.C. at: (202) 808-8858.

12<sup>th</sup> Annual *WORLD Symposium*, March 1 – 4, 2016 at Manchester Grand Hyatt, San Diego, California, 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, California, USA. Contact FSIG for more information: <http://www.fabry.org/FSIG.nsf/Pages2/HomePage>

American College of Medical Genetics and Genomics (ACMG) 2016 Annual Clinical Genetics Meeting, March 8 - 12, 2016, Tampa Florida, Tampa Convention Center. Visit: <http://www.acmgmeeting.net/acmg2016/Public/enter.aspx>

Society for Inherited Metabolic Disorders (SIMD) 39<sup>th</sup> Annual Meeting: April 3 - 6, 2016 at Sawgrass Golf Resort & Spa, Ponte Vedra Beach, Florida, USA. **Travel Award Abstract submission deadline: December 2, 2015.** Regular Abstract submission deadline: December 7, 2015. Details of this meeting: <http://www.simd.org/Meetings/SIMD2016/Info.asp>

NTSAD's 38<sup>th</sup> Annual Family Conference will be held April 7 – 10, 2016 in Orlando, Florida at the Rosen Shingle Creek hotel. Visit: <http://www.ntsad.org/index.php/event-listings/family-conference/2016-family-conference>

Society for the Study of Inborn Errors of Metabolism's SSIEM Academy 2016, April 18 – 19, 2016 in Freidburg, Germany. Details at: <http://www.ssiem.org/home/welcome.asp>



The Penn Medicine Orphan Disease Center (ODC) will host the 3<sup>rd</sup> Annual Million Dollar Bike Ride on Saturday, May 7<sup>th</sup>, 2016 to raise money for rare disease research. The National Tay-Sachs and Allied Diseases Foundation has their stellar "Team NTSAD" participating each year. The funds raised by Team NTSAD will go to fund the NTSAD's 2016 Million Dollar Bike Ride Pilot Grant Program. Visit: <http://www.milliondollarbike.ride.org/> or contact Samantha Charlestone at: [scharle@upenn.edu](mailto:scharle@upenn.edu) or phone (215) 573-6822.

The International MPS Network's 4<sup>th</sup> 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](http://www.MPS2016.com). Meeting at Hotel Maritim Bonn (<http://www.maritim.com/en/hotels/germany/hotel-bonn/hotel-overview#>)

Society for the Study of Inborn Errors of Metabolism 2016 Annual Symposium, September 6 - 9, 2016 in Rome, Italy, at Palazzo dei Congressi, Piazza John Fitzgerald Kennedy, 1 00144 ROMA. E-mail to: [info@ssiem2016.org](mailto:info@ssiem2016.org). Visit: <http://www.ssiem2016.org/>

The National Fabry Disease Foundation's 2016 Fabry Family Medical Conference will be held September 8 – 9, 2016. Their 2016 Charles Kleinschmidt Fabry Family Camp will be held September 9 – 11, 2016. Both events are held at Victory Junction camp near Greensboro, NC. Read the article in the October 2015 issue of "Indications" about the National Fabry Disease Foundation for detailed information, and visit: <http://www.fabrydisease.org/>

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

## Important Step Achieved by Lysogene

Lysogene, a leading French clinical-stage biotechnology company, has announced that the FDA has granted *orphan drug* designation and *rare pediatric disease* designation to its agent LYS-SAF-302, a potential gene therapy treatment for patients with Sanfilippo syndrome type A (MPS IIIA). Lysogene is planning an upcoming multinational phase II/III clinical trial of this agent. The aim of this trial is to determine that the treatment is effective and to further confirm its safety.

For more information, visit: [www.lysogene.com](http://www.lysogene.com).

## Indications™

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