Indications™

Newsletter of The Lysosomal Disease Network™

May 2014 **Vol. 1, No. 6**

Keys to Understanding the Lysosomal Disease Network

Can patient advocacy groups conduct rare disease research jointly with the LDN? Are there any examples of this?

By Evelyn S. Redtree, M.S.

Looking ahead to the five-year renewal of the Lysosomal Disease Network's NIH funding, two patient advocacy groups have already partnered with the LDN to jointly conduct research in ultra-orphan diseases during the new funding cycle. The LDN encourages direct contact from all patient advocacy groups interested in engaging in joint research. To begin exploring the possibilities, contact the LDN's Informatics Director, David Erickson, requesting him to make an appointment for a phone conversation with the LDN's Principal Investigator, Dr. Chester Whitley. David Erickson can be e-mailed at: gtadmin@umn.edu.

Hunter's Hope Foundation, a Krabbe disease patient advocacy group, will be collaborating with the LDN in a pilot study entitled "Long term follow up for Krabbe disease," whose Principal Investigator will be Thomas Langan, M.D., Associate Professor of Neurology, Pediatrics, Physiology, and Biophysics, University of Buffalo School of Medicine; Director of

(Continued on Page 2)

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 . . .

Hunter's Hope Foundation

http://www.huntershope.org/site/PageServer

Hunter's Hope Foundation was established in 1997 by Jim and Jill Kelly, after their infant son Hunter (2/14/97-8/5/05) was diagnosed with Krabbe disease, one of the leukodystrophies. Hunter's Hope Foundation was established to address the unmet need for information and for medical research in Krabbe disease and related leukodystrophies. The Foundation also supports and encourages those affected and their caregivers as they struggle to cope and adjust to the demands of these inherited lysosomal diseases.

(Continued on Page 7)

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

Can patient advocacy groups conduct rare disease research jointly with the LDN? Are there any examples of this?

(Continued from Page 1)

the Headache and Concussion Clinics and Co-Director of the Pediatric MS Clinic at Children's Hospital of Buffalo; and Clinical Director of the Hunter James Kelly Research Institute (HJKRI). The specific aims of this pilot study are to assess long-term developmental outcomes in children with positive newborn screens for Krabbe disease, as well as to assess long-term functional outcomes in these children. This study will use telephone interviews to examine these outcomes. A previous LDN pilot study (protocol number 6710) used telephone interviews to carry out their work; this new pilot study will build upon that method.

Key to this study is to determine whether children with very low galactocerebrosidase (GALC) enzyme activity, but no clinical evidence of Krabbe disease, are at risk for developmental and functional delays. This technique may serve as a surrogate tool in place of more costly comprehensive neuropsychological testing.

All infants identified as having low GALC enzyme activity in New York state's program of universal newborn screening will be entered into the study. These will include all New York children who are asymptomatic or pre-symptomatic and whom are currently enrolled in the Krabbe World Wide Registry, as well as any newly diagnosed children during the 5-year study period.

In Krabbe disease, 85-90% of affected persons have an infantile-onset form of the disease. Other forms of Krabbe disease, however, can occur throughout life. Unfortunately, neither GALC enzyme activity levels nor identification of a specific genetic mutation reliably predict which Krabbe disease phenotype can be expected in an infant identified through New York's universal newborn screening program. Since the only treatment for Krabbe disease is umbilical cord blood stem cell or bone marrow transplantation during infancy, it is crucial to be able to distin-

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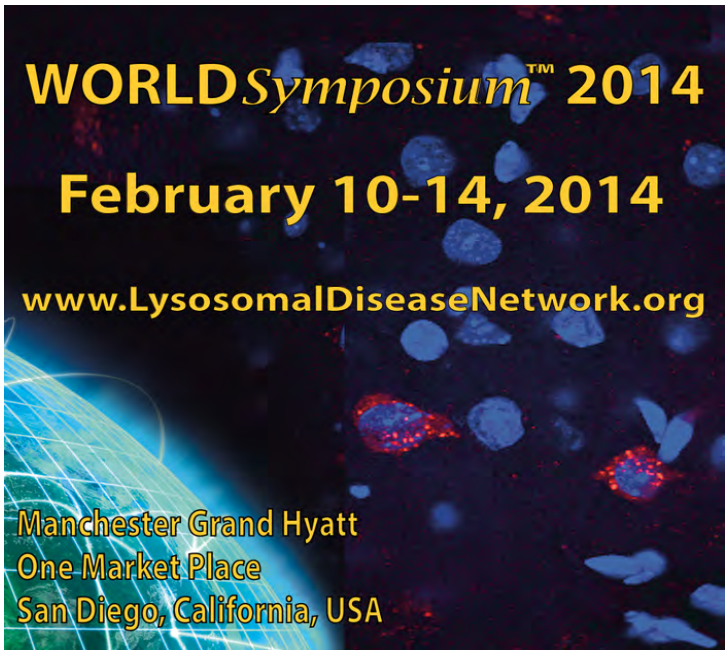

The 10th Annual WORLD*Symposium*™ Highlights in Review: Part III

The 10th annual WORLD*Symposium* 2014 presented platform presentations focused on clinical trials on Thursday, February 13th. Twenty-six researchers presented the findings of their studies, including Barry Byrne and colleagues of the University of Florida School of Medicine in Gainesville, Florida; Kansas University Medical Center in Kansas City, Kansas; University of California San Diego Health System; SA Pathology in Adelaide, Australia; Le Centre Hospitalier de Nice in Nice, France; Royal Brisbane and Women's Hospital in Brisbane, Australia; University Hospital Birmingham in Birmingham, UK; Royal Free & University College Medical School in London, UK; Hôpital Pitié-Salpêtrière in Paris, France; Johannes-Gutenberg-University Mainz in Mainz, Germany; Salford Royal NHS Foundation Trust in Salford, UK; and BioMarin Pharmaceutical in Novato, California. They investigated BMN 701, a drug for treatment of late-onset Pompe disease patients. BMN 701 is a novel chimeric fusion protein of insulin-like growth factor 2 (IGF-2) and acid α-glucosidase (GAA), and is designed to reduce glycogen storage in striated muscle. In preclinical studies BMN 701 cleared glycogen in heart, diaphragm, and skeletal muscles at a lower dose than alglucosidase-α (rhGAA).

(Continued on Page 4)

Can patient advocacy groups conduct rare disease research jointly with the LDN? Are there any examples of this?

(Continued from Page 2)

guish the infantile-onset forms from later-onset forms. At this time the literature is limited regarding Krabbe disease clinical signs and symptoms, age of onset, and survival of persons with the later-onset forms. There also is literature on the results of neurodiagnostic studies in Krabbe disease, but again, it is limited. It is thus important to determine in a population of children who have been diagnosed with varying forms of the disease, which (if any) of these findings is predictive of phenotype.

As the result of the LDN's collaboration in this study, the data obtained under the protocol will be entered into the Rare Diseases Clinical Research Network's Data Management and Coordinating Center (DMCC) and the NIH-sponsored dbGAP (database of genotypes and phenotypes). The protocol will be registered with ClinicalTrials.gov, and all publications will be subject to the public access policy. The ability to deposit research data into a public database will allow other researchers interested in Krabbe disease to have access to this information and contribute to a greater understanding of this ultra-orphan genetic disorder.

The patient advocacy group "Jonah's Just Begun" will be collaborating with the LDN in the pilot study entitled "Natural history study for MPS IIIC and MPS IIID." Paul Levy, M.D., Assistant Professor of Pediatrics and Pathology; Director, Center for Inherited Metabolic Disorders; Director, Biochemical Genetics Laboratory; and Site Director, NY State Newborn Screening Referral Site for Inherited Metabolic Disease, all at Einstein/Montefiore Medical Center in New York City, will be Principal Investigator of this new pilot study. The overall aim of this project is to expand knowledge of the clinical features of the ultra-orphan diseases MPS IIIC and MPS IIID by carrying out a prospective natural history study. Fifteen patients with MPS IIIC, and two patients with MPS IIID have been identified for this study. During the course of the study, the genotype and the residual enzyme activity levels will be determined. Outcome measurements will be obtained periodically thourgh neurocognitive testing; by measuring glycosaminoglycans in urine; by observing clinical status; and by obtaining brain images, to document the disease course. The investigators' hypothesis is that disease progression will be manifested by neurocognitive decline that will correlate with genotype and/or residual enzyme activity, and with an increase in glycosaminoglycan levels in urine.

The first specific aim of this study is to document the clinical course of the diseases. Standardized neuropsychological testing will be administered to document the cognitive status of patients and correlate this with their disease status. Cognitive regression over time will be documented by following longitudinal changes of the neuropsychological testing. MRI images will be obtained to observe changes in brain structure over time, including myelination, ventricular size and cortical atrophy. Brain volumetrics and diffusion tensor imaging (DTI) will be performed to quantify these changes over time in patients with Sanfilippo syndrome types C and D.

The second specific aim of this pilot study is to evaluate biomarkers as correlates to disease status. Residual enzyme activity (in leukocytes or fibroblasts) will be measured, with an attempt to correlate the findings with genotype and disease progression. Urinary glycosaminoglycans will also be measured, with an attempt to correlate these findings with disease progression.

The third specific aim of this pilot study is to compare the resulting data with other studies of Sanfilippo syndrome patients to help better delineate the phenotypes and differences between types MPS IIIC and IIID, and types MPS IIIA and IIIB.

As with the pilot study collaboration with Hunter's Hope Foundation, as a result of the LDN's collaboration in this study, the data obtained under the protocol will be entered into the Rare Diseases Clinical Research Network's Data Management and Coordinating Center (DMCC) and the NIH-sponsored dbGAP. The protocol will be registered with ClinicalTrials.gov, and all publications will be subject to the public access policy. The ability to deposit research data into a public database

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will allow other researchers interested in Sanfilippo syndrome types C and D to have access to this information and contribute to a greater understanding of this ultra-orphan genetic disorder.

Shire Demonstrates Its Compassion for Sanfilippo Syndrome Patients

Shire has voluntarily shared the design of the case report forms used in its MPS IIIA natural history study. These have been shared with Dr. Paul A. Levy, M.D., FACMG, who will lead a new Lysosomal Disease Network research study after renewal of the LDN's NIH funding. Dr. Levy's new study will be entitled "Natural History Study for MPS IIIC and MPS IIID."

Shire's research cooperation makes it possible to centrally compile a much larger amount of Sanfilippo syndrome natural history data. Eventually, this may be used by researchers to compare apples-to-apples across multiple studies and multiple types of MPS III, facilitating swifter progress towards development of effective treatments for Sanfilippo syndrome patients. The Lysosomal Disease Network recognizes and sincerely thanks Shire for their assistance.

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

(Continued from Page 2)

Previously, preliminary safety and efficacy results were described from a 24-week Phase 1/2 study in patients with late-onset Pompe disease treated with BMN 701 every other week. This has now been followed by an extension study of patients who completed that preliminary 24-week safety and efficacy study. Primary objectives of the extension study included evaluation of safety and antibody response to BMN 701 and IGF1 and IGF2. As of 9-23-2013, patients in the extension study had maintained their initial improvement in respiratory muscle strength as measured by maximum inspiratory and maximum expiratory pressure, and in their endurance as measured by the 6-minute walk test (mean increase of 22.3 meters). Hypoglycemia, an anticipated pharmacologic effect, was observed in the majority of patients at the 20 mg/kg dose, but was transient and managed by oral and IV caloric intake without sequelae. The investigators concluded that these extension study results support ongoing evaluation of BMN 701 in patients with late-onset Pompe disease. Their abstract is #38 in the *Molecular Genetics & Metabolism* February 2014 issue.

A BioMarin Pharmaceutical Inc. Phase 3 switchover study is currently enrolling late-onset Pompe disease patients 18 years and older who have received prior treatment with commercial rhGAA for at least 48 weeks. To be eligible, patients must not have diabetes or other disease known to cause hypoglycemia.

Also currently enrolling is a long-term study for extended BMN 701 treatment of patients with Pompe disease who have completed previous BMN 701 studies. This study of patients with Pompe disease will evaluate the long-term safety and efficacy of BMN 701 administered by IV infusion every 2 weeks. For further information about both of these studies, visit: http://www.bmrn.com/pipeline/clinical-trials/pompe.php. Also, search for these studies at ClinicalTrials.gov under their identifier numbers NCT01924845 and NCT-01435772.

(Continued on Page 5)

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

(Continued from Page 4)

Simon Jones and colleagues at Manchester Centre for Genomic Medicine, St. Mary's Hospital, CMFT, and University of Manchester in Manchester, UK; Mount Sinai School of Medicine, New York City; Genzyme, a Sanofi company, in Cambridge, Massachusetts; The National Institute for Health Research/Wellcome Trust Clinical Research, Central Manchester University Hospitals NHS Foundation Trust, in Manchester, UK reported the preliminary results of an ongoing open-label, multicenter, ascending-dose study of the tolerability and safety of recombinant human acid sphingomyelinase (rhASM) in patients with ASM deficiency (ASMD), also called Niemann-Pick disease type B (NPDB). Their study was funded by Genzyme, a Sanofi company.

Patients with NPDB accumulate sphingomyelin within multiple cell types, particularly within hepatocytes and macrophages of the reticuloendothelial system, which leads to hepatosplenomegaly, liver fibrosis, interstitial lung disease, thrombocytopenia and anemia. While administration of rhASM reduced sphingomyelin levels in ASM knockout mice across a range of doses, high doses of rhASM induced an acute toxicity resulting in changes in cardiovascular hemodynamics, systemic inflammatory response and ultimately death in ASM knockout mice, but not in normal mice. The toxicity was prevented by debulking the sphingomyelin with several low doses of rhASM prior to a high dose, thereby implicating the rapid production of pro-inflammatory metabolites of sphingomyelin as the cause of the toxicity.

The primary objective of their Phase 1b study (ClinicalTrials.gov identifier number NCT01722526) is to determine the safety and tolerability of within-patient dose escalation of rhASM administered intravenously every two weeks for 26 weeks. Five adult NPDB patients were enrolled in this ongoing multiple ascending-dose study. The dose is increased provided the patient experiences no or mild adverse events at the current dose level. Patients are monitored in the hospital prior to and for at least 72 hours post-dose throughout dose escalation; thereafter they are maintained at their maximum tolerated dose until the end of the 26-week study period. Study assessments include continuous adverse events reporting and periodic evaluations of safety, pharmacokinetics, pharmacodynamics, and efficacy parameters. To date, all 5 patients have successfully escalated to ≥1.0 mg/kg, and 3 patients have reached 3 mg/kg. Adverse events have been mild or moderate, with those considered related to rhASM administration generally occurring between 12 and 48 hours post-dose. To date no serious adverse events have been reported. Preliminary results from this ongoing study suggest that within-patient dose-escalation may improve the tolerability of higher doses of rhASM by gradual debulking of sphingomyelin. Their abstract is #112 in the *Molecular Genetics & Metabolism* February 2014 issue.

William S. Sly of St. Louis University School of Medicine in St. Louis, Missouri presented results from the research work of Joyce E. Fox of Steven and Alexandra Cohen Children's Medical Center in New York City, Emil D. Kakkis of Ultragenyx Pharmaceutical Inc. in Novato, California, and himself concerning enzyme replacement therapy for MPS VII, also called Sly syndrome (Dr. Sly is the first to describe this disease). Sly syndrome is a very rare lysosomal disease caused by deficiency of β-glucuronidase (GUS), required for the degradation of dermatan sulfate and heparan sulfate. Two decades of animal research have demonstrated effective treatment with enzyme replacement therapy in MPS VII mouse models, yet there is no enzyme replacement product approved for treatment of MPS VII patients.

Dr. Sly presented the clinical features of the first MPS VII patient who, on an emergency basis, was recently infused with recombinant human GUS (rhGUS) as enzyme replacement therapy. (This rhGUS is designated as study drug UX003). The patient is a 12 year-old boy diagnosed with MPS VII by fibroblast assay, consistent with the clinical features including hydrops fetalis, hepatosplenomegaly, heart valve disease, frequent sinopulmonary infections and upper airway obstruction, declining pulmonary function, dysostosis multiplex, and spinal cord compression requiring cervical fusion. His baseline urinary glycosaminoglycan (GAG) levels were significantly elevated, at four times the

(Continued on Page 6)

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

(Continued from Page 5)

upper limit of normal. Despite a tracheostomy, nocturnal CPAP and oxygen therapy, significant pulmonary restriction and obstruction led to oxygen dependence, rising CO_2 levels in the 60-80 range, approaching respiratory failure, and the need for full-time ventilation. Since no additional medical measures could improve his function, the investigators implemented experimental enzyme replacement therapy by infusing rhGUS at 2 mg/kg over 4 hours every 2 weeks, after pretreatment with an oral antihistamine.

To evaluate his response to therapy, urinary GAG levels, pulmonary function, oxygen dependence, CO_2 levels, cardiac valve function, liver and spleen size, and growth velocity are being assessed. Safety is being evaluated by standard assessments and observance of any infusion-related reactions. Dr. Sly reported their data on efficacy and safety of rhGUS infusion in this first report of enzyme replacement therapy in an MPS VII patient. The patient has responded well to this treatment, with measured improvements that have resulted in greatly increased quality of life. Their abstract is #76 in the *Molecular Genetics & Metabolism* February 2014 issue.

Ultragenyx Pharmaceutical Inc. has an ongoing open-label Phase 1/2 study to assess the safety, efficacy, and dose of study drug UX003. The goal is to recruit up to five subjects with MPS VII. This study's principal investigator is Simon Jones, M.D. of the University of Manchester in the UK. For details, search for this study on ClinicalTrials.gov under its identifier number: NCT01856218.

Marc C. Patterson and colleagues of the Mayo Clinic in Rochester, Minnesota; Villa Metabolica, University of Mainz in Mainz, Germany; Academic Medical Centre, University of Amsterdam in Amsterdam, Netherlands; INSERM Unit 820 in Lyon, France; Actelion Pharmaceuticals Ltd. in Allschwil, Switzerland; Numerus Ltd. in Sandhurst, UK; and Hospital Sant Joan de Déu in Barcelona, Spain presented their longitudinal data from the international registry for Niemann-Pick disease type C (NPC). Specifically, they looked at data collected between September 2009 and August 2012 for NPC patients who received miglustat continuously between enrollment and last follow-up visit. Patient demographics, disease characteristics and treatment data were collected, and disability status was evaluated using a scale that rated ambulation, manipulation, language and swallowing from 0 (normal) to 1 (worst). Patients were categorized as 'improved/stable' if ≥3 out of these 4 domain scores were lower or unchanged between enrollment and last follow-up visit, or as 'progressed' if <3 domain scores were lower or unchanged.

Their results showed that a total of 52/72 (72%) of patients were categorized as 'improved/stable', while 20/72 (28%) were categorized as 'progressed'. Safety and tolerability findings for miglustat were in line with previously published data. A low proportion of patients had chronic diarrhea during follow-up (7.6%). Disability status was improved or stable in the majority of miglustat-treated patients. Their abstract is #191 in the *Molecular Genetics & Metabolism* February 2014 issue.

Among the exciting posters exhibited was that of Einat Almon and colleagues of Protalix Biotherapeutics in Carmiel, Israel. Their poster of Abstract #12 presented their research of PRX-102, a chemically modified, plant-cell expressed recombinant human α-GAL-A enzyme (prh-α-GAL-A), which is being developed by Protalix Biotherapeutics as an enzyme replacement therapy for the treatment of Fabry disease (α-galactosidase deficiency). In this study it was demonstrated that the modified enzyme, PRX-102, is active and localizes to the intracellular target organelles, the lysosomes, in cells derived from Fabry patients. When compared to commercially available enzyme replacement therapy (agalsidase-α and agalsidase-β, which are comprised of recombinant human α-GAL-A expressed in mammalian cells), PRX-102 presents comparable kinetic properties with higher stability in vitro both in plasma and simulated lysosomal conditions. Studies using a Fabry mouse model revealed significantly extended circulation residence time for PRX-102 in comparison with the commercial product, and higher activity of the enzyme for a prolonged period of

(Continued on Page 7)

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

(Continued from Page 6)

time in target organs in vivo. Furthermore, PRX-102 was shown to induce significant reduction of lobotriaosylceramide accumulation in target tissues. The extended circulation time together with the higher activity of PRX-102 in target organs over time, relative to the commercial drugs, have the potential for a more efficient enzyme replacement therapy for the treatment of Fabry disease. PRX 102 is now under evaluation in clinical studies in Fabry patients. To learn more about these studies, search for Clinical Trials.gov identifier numbers NCT01981720, NCT017-69001 and NCT01678898.

This concludes the review of the highlights of WORLD *Symposium* 2014. The February 2015 issue of *Molecular Genetics & Metabolism* will be an entire issue focusing on lysosomal diseases. The deadline for submission of articles for this issue is September 1, 2014. Be sure to write 'for the February 2015 lysosomal diseases issue' prominently in your submission.

The deadline for abstract submission for WORLD*Symposium* 2015 is October 1, 2014. Details of abstract submission will be available at ***LysosomalDiseaseNetwork.org*** in the coming months. Please join us in Orlando, Florida at the Hyatt Regency Orlando hotel for WORLD *Symposium* 2015 from February 9–12, 2015. See you there!

Meet Our Patient Advocacy Groups

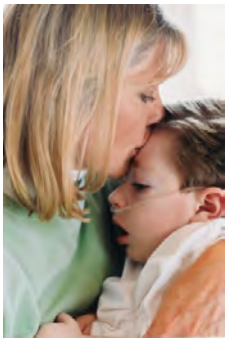
(Continued from Page 1)

Hunter's Hope Foundation has defined its mission as:
• To broaden public awareness of Krabbe disease and other leukodystrophies, thus increasing the probability of early detection and treatment.
• To gather and provide current, functional information and service linkages to families of children with leukodystrophies.
• To fund research efforts that will identify new treatments, therapies and ultimately, a cure for Krabbe disease and other leukodystrophies.
• To establish an alliance of hope that will nourish, affirm and confront the urgent need for medical, financial and emotional support of family members and those affected with leukodystrophies.

To achieve the Foundation's goal of funding research into the cause, prevention, treatment and clinical care for children suffering from Krabbe disease and other leukodystrophies, Hunter's Hope entered into an agreement in 2008 with the University at Buffalo School of Medicine, to create the Hunter James Kelly Research Institute (HJKRI). The mission of the HJKRI is to find better treatments and ultimately, a cure for those suffering from Krabbe disease or other leukodystrophies. All Foundation-funded research, including both basic and clinical science, is coordinated through the Institute, which is located in the New York State Center of Excellence in Bioinformatics and Life Sciences (CoE), a prominent part of the Buffalo Niagara Medical Campus. There are multiple hyperlinks on the Foundation's Web site to access extensive information about HJKRI, as well as its research publications.

Hunter's Hope Foundation has joined forces with the Lysosomal Disease Network to strengthen and facilitate a HJKRI study gathering natural history data to assess long-term developmental and functional outcomes in children with positive newborn screens for Krabbe disease. This study is discussed further in the "Keys to Understanding the LDN" article, specifically on pages 2 and 3 of this issue of "**Indications**."

Jacque L. Waggoner joined Hunter's Hope Foundation in October of 1997, serving as Chairman of the Board. Ms. Waggoner is the grandmother of Hunter James Kelly. The Foundation's Board of Directors appointed Jacque Waggoner to Chief Executive Officer of the Foundation in July 2007. Under Ms. Waggoner's leadership, Hunter's Hope has awarded over $15 million to leukodystrophy and other neurological disease-related research.



Jacque L. Waggoner and Hunter James Kelly

(Continued on Page 8)

Meet Our Patient Advocacy Groups

(Continued from Page 7)

Ms. Waggoner's background includes earning a bachelor's degree in mathematics from the University at Buffalo, and teaching middle- and high-school mathematics. Subsequently she worked in information technology management positions in various non-profit and for-profit organizations in the Buffalo, NY region.

Andrea L. Moran began working for the Foundation in July of 2007, beginning as the Special Event Coordinator. During the next several years, Andrea grew within the Foundation, overseeing the development department and taking responsibility for the Foundation's fundraising efforts, as well as marketing and public relations. Ms. Moran was appointed Executive Director of Hunter's Hope Foundation in April 2013.

Andrea Moran with Marcus Mattina at the 2013 Hunter's Hope Family & Medical Symposium. Marcus was diagnosed with Krabbe disease and received an umbilical cord blood stem cell transplant in 2008, just a few weeks after he was born. He is now 5 years old and started Kindergarden this year.

Due in large part to a college internship with the Buffalo, NY chapter of the March of Dimes, Andrea became passionate about work in the non-profit sector. Her passion is to ensure that all children have a healthy life from the start, and to serve families affected by severe medical conditions for which research, advocacy and support programs improve quality of life. Ms. Moran exercises her involvement across all areas of Hunter's Hope Foundation, guiding the organization in funding research for better treatments and a cure for Krabbe disease and other leukodystrophies, coordinating numerous programs to support affected families, and working diligently to advocate on state and federal levels for expanded and universal newborn screening for the leukodystrophies and other lysosomal diseases.

A major goal of the Foundation is for all newborns to be tested through a universal newborn screening program for all diseases, when early detection and treatment can save the life of a child. Through its efforts, combined with the work of many dedicated people, on August 7, 2006 New York state became the first state in the U.S. to launch a newborn screening program for Krabbe disease. This means that every child born in New York is screened for Krabbe disease within a few days after birth. If the screen is positive, infants will have the opportunity to be treated with an umbilical cord blood transplant, and have the possibility of living a long, healthy life.

The doctors at Duke University Hospital in Durham, North Carolina (http://www.dukemedicine.org/locations/duke-university-hospital) are national leaders in providing treatment for leukodystrophies through umbilical cord blood stem cell and bone marrow transplantation. Patients receiving transplants must stay near Duke University Hospital from six months to a year while having regular post-transplant follow-ups. Since 2005, Hunter's Hope Foundation has provided a 'home away from home' for families receiving treatment at Duke, and has a joint venture with the Ronald McDonald House of Durham. They have partnered to provide leukodystrophy families receiving treatment at Duke University Hospital with the comforts of home at no cost to the families. Located on the Duke University campus and just minutes from Duke University Hospital, the "Hunter's Home" program provides to families receiving treatment at Duke a fully-furnished home environment. Comforts of the home environments include private bedrooms, inviting community spaces, daily home-cooked meals and a stocked kitchen, a playroom, computer room and laundry facilities, as well as a network of support through interactions with other leukodystrophy families, paid staff, and volunteers. For more information about the "Hunter's Home" program, visit: http://www.huntershope.org/site/PageServer?pagename=familyprograms_huntershomes. Donations to specifically support this crucial program can also be made using the link on that Web site.

The Foundation maintains an "Affected Family Registry" with easy sign-up on their Web site. The purpose of the registry is to gather data to prove higher prevalences of these diseases, to assist in the struggle for expanded and universal newborn screening for leukodystrophies. To sign up, visit: http://www.huntershope.org/site/PageServer?pagename=familyprograms_affectedfamilyregistration.

(Continued on Page 9)

Meet Our Patient Advocacy Groups

(Continued from Page 8)

Hunter's Hope "Equipment and Supply Exchange" program has been designed to help fulfill the equipment or supply needs of Krabbe disease and leukodystrophy children, as well as help families place equipment and supplies that they are no longer using. Hunter's Hope covers the shipping cost to place the equipment with the family in need. Links on their Web site make this an easily initiated process. The Foundation also offers downloadable information sources including "Hope for Life - Family Resource Guide," "Krabbe Newborn Screening," and hyperlinks to information-rich Web sites such as "Caring 4 Krabbe Kids - A Resource for Families Dealing With Krabbe Disease."

The Foundation's program "Hunter's Wish Gift" helps families who face extreme financial stress attributed to the costs associated with caring for a child with Krabbe disease or another leukodystrophy. Requests are granted on a case-by-case basis and are limited to meeting needs that will enable an affected family to provide the best possible care for their child. Families come to the Foundation for assistance with a unique need – travel expenses associated with treatment, a wheelchair lift to enable a family to safely travel with their child, or assistance in purchasing a vehicle to accommodate their child's equipment needs. These are only a few examples of ways "Hunter's Wish Gifts" have helped leukodystrophy families focus on what matters most – caring for their child. Contact is easily initiated through the Foundation's Web site.

In conjunction with the independent organization 'Kaden's Kisses,' through Hunter's Hope Foundation, an established family program is operated to help alleviate some of the financial burden faced by families who are recently bereaved by the death of their child. The application for financial assistance is downloadable from the Hunter's Hope Foundation Web site.

Hunter's Hope Foundation annually convenes a multidisciplinary workshop in the Buffalo, New York area entitled "Family & Medical Symposium." This week-long event begins by bringing together for a half-week, in a conference-style setting, child neurologists, neuropsychologists, neuroradiologists, stem cell transplantation physicians, basic scientists, geneticists, neurodevelopmental pediatricians, oncologists and experts in newborn screening to discuss advances in basic and clinical medical research in Krabbe disease and other leukodystrophies. Attendance at the scientific and medical symposium is by invitation only. Interested persons should e-mail the Foundation to explore their interest further. Hunter's Hope Foundation covers air and ground transportation, lodging, meals and conference fees for all these attending professionals.

During the second half of the week, affected families gather to gain in-depth information about leukodystrophies, learn about the latest developments in medical research and patient care, identify available resources, develop and nurture mutual support systems, and share numerous fun activities and outings. Some of the researchers and physicians stay for the family portion of the week. Hunter's Hope Foundation covers ground transportation between airport and hotel, conference fees, lodging, meals and snacks for all families. They also offer a travel scholarship for which families can apply (the "Hunter's Hope Helping Hand Grant Travel Assistance" program). The 17th Annual Hunter's Hope Family & Medical Symposium is scheduled for Sun. July 27 - Wed. July 30, 2014. It will convene at Holiday Valley Resort in Ellicottville, NY. For more details, visit: http://www.huntershope.org/site/PageServer?pagename=familyprograms_symposium.

Hunter's Hope Foundation has an extensive Web site that is too vast to be completely described in the pages of "**Indications**." Some realms of the site not covered here include the Krabbe World Wide Registry, fund raising, public service announcements and media relations, universal newborn screening, and leukodystrophy explanatory information. The reader is encouraged to visit the site and explore the information available there: http://www.huntershope.org/site/PageServer.

LDN Research *Matters*

Protocol #6716: Genotype-Phenotype Correlations of Late Infantile Neuronal Ceroid Lipofuscinosis

In the April issue of "**Indications**," LDN protocol number 6717 entitled "Clinical and neuropsychological investigations in Batten disease" was presented and its Principal Investigator Jonathan Mink, M.D. was profiled. In this issue we continue with a focus on Batten disease research funded by the LDN.

Lysosomal Disease Network pilot study number 6716, led by Douglas J. Ballon, Ph.D. of Weill Cornell Medical College in New York City, seeks to assess the genotype–phenotype correlations and the progressive central nervous system (CNS) deterioration inherent in late infantile neuronal ceroid lipofuscinosis (LINCL). LINCL is a form of Batten disease. The correlation analysis will be made between genotype (genetic constitution) and the baseline and 18-month phenotypes. The correlation analysis will also be made between genotype and rate of CNS decline.

The affected children, aged 2-18 years, will be assessed for a number of neurological and imaging parameters. The study will be carried out in children diagnosed with LINCL in the early stage of the disease (score of 4-10 on the "Weill Cornell LINCL scale"). Each individual undergoes a baseline evaluation that includes: (1) a general assessment (medical history, physical exam, vital signs, respiratory rate, temperature and weight, neurological assessment); (2) ophthalmological assessment (eye exam); (3) general blood analysis (chemistry, hematology and coagulation); (4) blood sample collection for CLN2 (Batten disease) genomic analysis; (5) urine analysis; (6) MRI/MRS assessment; (7) a lumbar puncture (spinal tap) for cerebrospinal fluid analysis; (8) and developmental psychological assessment consisting of these scales: the Weill Cornell LINCL scale, the standardized Child Health Questionnaire and ITQOL quality-of-life scale, and the Mullen scale. In addition to providing the data needed to carry out this LDN study, the results of this baseline evaluation provide a basis for determining eligibility for some non-LDN-funded gene-transfer safety studies also being carried out by researchers at New York-Presbyterian/Weill Cornell Medical College. Dr. Douglas Ballon is also involved in these safety studies. (To learn more about these gene-transfer studies, search for the following ClinicalTrials.gov identifier numbers at the Clinical Trials.gov Web site: NCT01161576, NCT00151216, and NCT01414985. Read more also at: http://weill.cornell.edu/news/pr/2008/05/newyork-presbyterianweill-cornell-gene-therapy-clinical-trial-yields-promising-results-for-batten-di.html.)

To learn more details about LDN protocol number 6716, search for its ClinicalTrials.gov identifier number NCT01035424 at: http://clinicaltrials.gov/ct2/search/index.

Publication resulting from LDN protocol number 6716:

J.P. Dyke, D. Sondhi, H.U. Voss, D.C. Shungu, X. Mao, K. Yohay, S. Worgall, N.R. Hackett, C. Hollman, M.E. Yeotsas, A.L. Jeong, B. Van de Graaf, I. Cao, S.M. Kaminsky, L.A. Heier, K.D. Rudser, M.M. Souweidane, M.G. Kaplitt, B. Kosofsky, R.G. Crystal, D.J. Ballon, Assessment of disease severity in late infantile neuronal ceroid lipofuscinosis using multiparametric MR imaging. AJNR Am J Neuroradiol 34(4) (2013) 884-889. PMCID: PMC3644851.

Meet the Principal Investigators

Douglas J. Ballon, Ph.D. of Weill Cornell Medical College is principal investigator of LDN protocol number 6716, "Genotype-phenotype correlations of late infantile neuronal ceroid lipofuscinosis." Upon renewal of the LDN's NIH funding contract, Dr. Ballon will lead the LDN study entitled "Biomarkers for disease severity and therapeutic response in LINCL." Dr. Ballon is Director, Citigroup Biomedical Imaging Center at Weill Cornell Medical College in New York City. Dr. Ballon originally trained as an experimental nuclear physicist and subsequently did his postdoctoral work developing applications and techniques for magnetic resonance imaging and spectroscopy

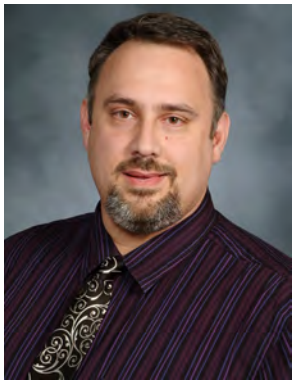
(Continued on Page 11)

Meet the Principal Investigators

(Continued from Page 10)

Douglas J. Ballon, Ph.D.

at Memorial Sloan-Kettering Cancer Center in New York City. He has over twenty-five years of experience in the development of imaging biomarkers for the detection, characterization, and therapeutic monitoring of disease. For the past eight years, Dr. Ballon's collaboration with Drs. Ronald Crystal and Dolan Sondhi's gene therapy laboratory at New York-Presbyterian/Weill Cornell Medical College has led to the first imaging-based whole-brain biomarker of Batten disease severity, and the first demonstration of viral vector-mediated CLN2 gene expression in the brain using a carotid artery delivery route. In 2001 Dr. Ballon became Founding Director of the Citigroup Biomedical Imaging Center at Weill Cornell Medical College, a $65 million comprehensive MRI, PET, SPECT, CT and optical imaging facility that currently supports over 60 research groups from 11 academic institutions.



Jonathan P. Dyke, Ph.D.

Dr. Ballon works closely with Dr. Jonathan P. Dyke, Ph.D., also of Weill Cornell Medical College, in conducting LDN protocol number 6716. Dr. Dyke will also be a co-investigator in Dr. Ballon's future LDN study entitled "Biomarkers for disease severity and therapeutic response in LINCL." Dr. Dyke is an imaging physicist with over fifteen years of experience developing imaging biomarkers for neurological and oncological applications. He has an extensive background in both magnetic resonance imaging and multiple pediatric clinical trials of gene therapy in LINCL (Batten disease).

Selected Douglas Ballon / Jonathan Dyke Publications:

J.P. Dyke, H.U. Voss, D. Sondhi, N.R. Hackett, S. Worgall, L.A. Heier, B.E. Kosofsky, A.M. Ulug, D.C. Shungu, X. Mao, R.G. Crystal, D.J. Ballon, Assessing disease severity in late infantile neuronal ceroid lipofuscinosis using quantitative magnetic resonance diffusion-weighted imaging. AJNR Am J Neuroradiol 28(7) (2007) 1232-1236. PMID: 17698521.

D. Sondhi, L. Johnson, K. Purpura, S. Monette, M. Souweidane, M.G. Kaplitt, B. Kosofsky, K. Yohay, D.J. Ballon, J. Dyke, S.M. Kaminksy, N.R. Hackett, R.G. Crystal, Long term expression and safety of administration of AAVrh.10hCLN2 to the brain of rats and non-human primates for the treatment of late infantile neuronal ceroid lipofuscinosis. Hum Gene Ther Methods 23 (2012) 324-335.

A. Santillan, D.G. Rubin, C.P. Foley, D. Sondhi, R.G. Crystal, Y.P. Gobin, D.J. Ballon, Cannulation of the internal carotid artery in mice: a novel technique for intra-arterial delivery of therapeutics. J Neurosci Methods 222 (2014) 106-110. PMID: 24269174.

Krabbe Disease Neuroimaging Study Yields New Avenue to Earlier Diagnosis

A.N. Abdelhalim, R.A. Alberico, A.L. Barczykowski, P.K. Duffner, **Patterns of magnetic resonance imaging abnormalities in symptomatic patients with Krabbe disease correspond to phenotype.** Pediatr Neurol 50(2) (2014) 127-134.

Ahmed N. Abdelhalim, M.D. of the Dept. of Neuroradiology, Roswell Park Cancer Institute, Ronald A. Alberico, M.D. and Amy L. Barczykowski, M.S. of the Dept. of Biostatistics, Population Health Observatory, University at Buffalo, and Patricia K. Duffner, M.D. of the Dept. of Neurology, Hunter James Kelly Research Institute, University at Buffalo School of Medicine (all at Buffalo, New York), performed a retrospective non-blinded study of symptomatic Krabbe disease patients' medical records and magnetic resonance imaging discs. They sought to learn whether magnetic resonance imaging abnormalities differed among Krabbe disease phenotypes.

Their results showed that early infantile patients (onset 0-6 months) had a predominance of increased intensity in the dentate/cerebellar white matter, and changes in the deep cerebral white matter. Later-onset patients (onset 13 months-10 years) did not demonstrate involvement in the dentate/cerebellar white matter, but had extensive involvement of the deep cerebral white matter, parieto-occipital region and

(Continued on Page 13)

Check Your Knowledge of Lysosomal Diseases

How well do you know Krabbe disease?

By Evelyn S. Redtree, M.S.

Krabbe disease, also known as globoid cell leukodystrophy, is caused by a deficiency of galactocerebrosidase, an essential enzyme for myelin metabolism. In humans, galactocerebrosidase is encoded by the GALC gene (cytogenic location 14q31). Krabbe disease has four types: early infantile Krabbe disease (EIKD), the most aggressive type; later-onset infantile; adolescent; and adult. The type is determined by the age of onset of symptoms. In rare cases it may be caused by a lack of active saposin A, a glycoprotein that stimulates the hydrolysis of glucosylceramidase. The lack of sufficient saposin A activity is caused by mutation of the PSAP gene (cytogenetic location 10q22.1). This form is designated as *atypical* Krabbe disease.

Krabbe disease most often affects infants (85%–90% of cases), with onset before age 6 months, but the later-onset forms can occur in adolescence or in adulthood. The symptoms of EIKD normally are not noticeable for the first weeks of life. For infants affected by EIKD, treatment must be administered as soon after birth as possible to avoid irreversible consequences. Without treatment, infantile-onset Krabbe disease is generally fatal before age 2 years.

Inheritance Patterns

Krabbe disease is inherited in an autosomal recessive manner. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of disease.

Incidence

In the U.S. Krabbe disease affects about 1:100,000 individuals. A higher incidence (6:1,000 people) has been reported in a few isolated communities in Israel (the founder effect).

Krabbe Disease Presentation

Krabbe disease is characterized by the presence of globoid cells (cells having multiple nuclei) that infiltrate the white matter of the brain; the progressive breakdown of nerves' protective myelin sheath, and brain cell destruction. Signs and symptoms of infantile-onset Krabbe disease may include irritability, unexplained fever, muscle hypertonicity with limb stiffness, seizures, feeding difficulties, vomiting, progressive neurologic deterioration with slowing of mental and motor development, and evidence of white matter disease revealed by neuroimaging. Other possible symptoms include muscle weakness, spasticity, deafness, optic atrophy, optic nerve enlargement, and blindness.

Later-onset Krabbe disease usually presents with weakness and vision loss, and regression of cognitive capacities. Although progression of the later-onset forms is slower than the infantile-onset forms, lifespan remains truncated. Affected individuals can appear clinically normal until vision loss, muscle weakness, and cognitive regression manifest. Even among siblings, the onset of symptoms and their clinical course can vary.

Prognosis

Prognosis may be significantly better for children who receive umbilical cord blood stem cells prior to symptom onset, or early bone marrow transplantation. Persons with juvenile- or adult-onset cases of Krabbe disease generally have a milder course of the disease and live significantly longer.

Treatment

There is no cure for Krabbe disease. Results of a very small clinical trial of patients with infantile-onset Krabbe disease found that children who received umbilical cord blood hematopoietic stem cell transplantation (HSCT) from unrelated donors prior to symptom onset subsequently developed with little neurological impairment. Results also showed that disease progression stabilized faster in patients who received umbilical cord blood HSCT, compared to those who received adult bone marrow transplantation. Bone marrow transplantation has been shown to

(Continued on Page 13)

Check Your Knowledge of Lysosomal Diseases

How well do you know Krabbe disease?

(Continued from Page 12)

benefit mild cases early in the course of the disease. Even so, although cognitive function might be improved or preserved with such treatment, peripheral nervous system function may still deteriorate. Later-onset forms demonstrate much clinical variability, confounding evaluation of treatment effectiveness. Otherwise, treatment for the disorder is palliative care for symptoms. Physical therapy may be helpful.

Acknowledgement

Some source information for the preceding article was provided by: Office of Communications and Public Liaison, National Institute of Neurological Disorders and Stroke, National Institutes of Health. Visit: http://www.ninds.nih.gov/disorders/krabbe/krabbe.htm.

Neuroimaging Study

(Continued from Page 11)

posterior corpus callosum. Late infantile-onset patients (onset 7-12 months) exhibited a mixed pattern; 40% had dentate/cerebellar white matter involvement while all had involvement of the deep cerebral white matter. Adolescent (onset 11-20 years) and adult (onset ≥21 years) patients demonstrated isolated corticospinal tract involvement.

The investigators concluded that neuroimaging abnormalities correspond to specific Krabbe disease phenotypes. Knowledge of these imaging abnormalities, when combined with typical clinical signs/symptoms, can be used to facilitate earlier diagnosis and delivery of appropriate treatment.

Calendar of Upcoming Events

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

International MPS Awareness Day is May 15, 2014!

Northwest MPS Family Day Meeting at Camp Korey, Saturday May 17, 2014, in Carnation, Washington, USA. Parents can focus on the educational program, while kids enjoy entertainment, diversions and interactions with Camp Korey's staff and volunteers. Speakers include Joseph Muenzer, M.D., Ph.D., of the Univ. of North Carolina School of Medicine; and the LDN's Kate Delaney of the Univ. of Minnesota. Visit: www. campkorey.org. Sponsored by Seattle Children's Hospital, with support from Biomarin; Genzyme, a Sanofi company; and Shire.

The Canadian MPS Society's 30th Anniversary National Family Conference, July 25 - 27, 2014 at Delta Bow Valley in Calgary, Alberta. Speakers include the LDN's Kate Delaney, of the University of Minnesota. For more information, visit: https://www.mpssociety.ca/page/events.aspx.

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

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

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

"360º Lysosome: from structure to genomics, from function to disease," October 23 - 28, 2014 in Izmir, Turkey. Course organizers/coordinators: Eser Y. Sozmen, M.D., Ph.D. and Michael Przybylski, Ph.D. Abstract submission deadline: June 20, 2014. For more information, visit: http://www.febs-lysosome.org/.

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

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