Indications™

Newsletter of The Lysosomal Disease Network™

October 2015 | *All past issues can be downloaded from the upper-right area of the LDN homepage at: www.LysosomalDiseaseNetwork.org* | **Vol. 2, No. 6**

LDN Fellowships Have Wide-Ranging Positive Effects

By Evelyn S. Redtree, M.S.

Each year of the LDN's NIH funding cycle, two post-doctoral Lysosomal Disease Network Fellows are selected, based upon their submitted applications. One LDN Fellowship is funded through LDN NIH funds. The University of Minnesota Medical School provides $50,000 matching funds for an additional postdoctoral Fellow, to be located at the University of Minnesota in the Twin Cities. Fellows are selected by the LDN Steering Committee, and can elect training in any clinically-related field such as clinical genetics, neurology, neuropsychology, or any field of medicine that might provide research or clinical service for patients with lysosomal disease. They are required to present their research at a major medical conference of their choosing, and at the recurring Conference on Clinical Research for Rare Diseases (CCRRD) presented by the Rare Diseases Clinical Research Network.

The LDN has a long track-record with its Fellowship program. The first Fellow was Julie Eisengart, Ph.D., who was mentored by Elsa Shapiro, Ph.D., at University of Minnesota during 2009-2010. Dr. Eisengart's Fellowship Research Project was entitled "Enzyme Replacement Therapy in Hurler Syndrome."

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In This Issue. . .

Meet Our Patient Advocacy Groups

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

National FABRY DISEASE Foundation

www.fabrydisease.org ❖ www.facebook.com/FabryDisease
www.twitter.com/FabryDisease1
www.YouTube.com/TheNFDF

By Evelyn Redtree, M.S., and Jerry Walter, M.S.

The February 2014 issue of "**Indications**" featured the Fabry Support and Information Group (FSIG), co-founded by its Executive Director, Jack Johnson (http://www.fabry.org/FSIG.nsf/Pages2/HomePage). Fabry disease patients are also served by the National Fabry Disease Foundation (NFDF), a non-profit IRS 501(c)(3) organization dedicated to supporting the Fabry disease community.

The NFDF was founded in 2005 by Jerry Walter, who is a retired U.S. Army Colonel who has Fabry disease.

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

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The National Fabry Disease Foundation

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Jerry Walter, M.S., Colonel, U.S. Army (Retired)

He is one of eighteen immediate and extended family members with Fabry disease, including four family members who have passed away under the age of 50 due to Fabry disease. Jerry is the NFDF's President as well as the only staff member, except for some occasional part-time help.

The NFDF defines its five primary functions as: assisting with Fabry disease education; facilitating Fabry disease identification to improve Fabry disease recognition and diagnosis; providing various forms of assistance to individuals with Fabry disease and their families; supporting Fabry disease research; and promoting advocacy for Fabry disease issues.

The NFDF continually works to increase the level of effort devoted to assisting and supporting people with Fabry disease. While increased effort is required in each of the NFDF's five primary functions, Fabry disease education and Fabry disease identification are its two highest priorities at this time. The NFDF believes it is critically important to educate healthcare providers, families and others to recognize this progressive, destructive and often life-threatening disease earlier in the disease process.

The NFDF's website at www.fabrydisease.org, a work in progress, their Facebook page and their e-newsletter are their main methods of communicating with the Fabry disease community to ensure everyone is aware of the NFDF's many programs and services. Jerry advised, "the NFDF's website is currently being rebuilt and should be ready for publication by the end of this year at the same website address." In the meantime, their 'old' website remains an excellent resource.

In addition to patients, family members and other supporters, the NFDF invites physicians and their staff members to sign up for the NFDF's e-newsletter in the "Connect With Us" section in the upper right-margin area of the NFDF homepage by clicking on the blue button labeled "Subscribe to our e-newsletter here."

The NFDF offers a 15-page downloadable .pdf handout entitled "National Fabry Disease Foundation Programs." This handout provides a snapshot of the NFDF's major programs and services in one easy-to-access document. Obtain it by visiting the NFDF website homepage, then look near the bottom of the page to find the rectangular program block labeled "National Fabry Disease Foundation Program Handout" and select the "Click to View" button. Contact the NFDF to obtain an electronic version for e-distribution. Jerry said, "no families should miss out on our valuable programs and services, and everyone can help to make that happen."

To provide the public with a better understanding of Fabry disease, the NFDF produced several Fabry disease education and awareness videos accessed via its You Tube channel: https://www.youtube.com/user/TheNFDF. The NFDF YouTube channel is also accessible on the website homepage in the Featured Programs section two-thirds down the homepage. Three new videos are being released this month. To be notified as new videos are released, subscribe to the NFDF You Tube channel. Their most viewed video to date is the Fabry Disease Symptoms video, which has been viewed over 10,000 times. One of the newest NFDF videos is being shown on more than 5,200 American Airlines flights in October and November 2015, potentially receiving over 250,000 views.

Through both improved Fabry disease education and thorough family-tree analyses, the NFDF is helping to find the thousands of individuals in the U.S. who are living with Fabry disease symptoms but are unaware they have Fabry disease. Once identified and diagnosed, individuals with Fabry disease can be empow-

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ered to make informed disease management and treatment decisions. See the article "LDN Research Matters" on page ___ in this issue, to understand why early diagnosis and early treatment is so important for persons who have Fabry disease.

The 2015 group of campers at the annual "Charles Kleinschmidt Fabry Family Weekend Camp" dodged some raindrops by having their portrait taken in the Victory Junction gymnasium. ‡

As one of their hallmark programs, the NFDF provides the "Charles Kleinschmidt Fabry Family Weekend Camp" held at Victory Junction camp in Randleman, North Carolina (near Greensboro) since 2010. Any family that has at least one child 6 to 16 years old who has Fabry disease is eligible to bring their entire immediate family to camp, expense-free. Travel to and from camp, lodging, meals, and fantastic family activities are all provided gratis to campers by the NFDF and its sponsors. Beginning in 2011, an educational conference was added to this event on Thursday and Friday before camp. The educational conference is open to all people with Fabry disease and their families, not just those attending camp. Transportation and lodging assistance is also available to conference attendees, depending upon current available resources. These events are made possible by charitable donations from the Kleinschmidt Family Foundation, Genzyme, Shire, Amicus and many generous individual sponsors.

‡ All photos are used with permission from every individual with Fabry disease and their family members included in the photos. -- Jerry Walter

Camp Volunteer Lisa Berry (holding umbrella), a genetic counselor from Cincinnati Children's Hospital, with two families at the 2015 camp.

Jerry said, "We provide transportation from all around the country, and with the NFDF's donation to Victory Junction camp, they provide lodging, meals, snacks, and loads of fun." Family applications to attend camp may be submitted beginning in July each year. The application process has a quite a few steps, and the NFDF needs to buy airline tickets as early as possible after each application is approved. They ask every family that is interested in attending to begin preparation for their application early. After completing the online application, kids with Fabry disease need a Victory Junction physical exam form signed by their physician, and all kids require immunization documentation according to Victory Junction's immunization policy. It is best to review immunization requirements at www.victoryjunction.org and get any required immunizations well before the official application process begins. If a family wishes to attend camp, their first step is to notify Jerry at: jerry.walter@fabrydisease.org to indicate their interest.

The 5th annual educational conference and 6th annual Charles Kleinschmidt Fabry Family Camp just concluded at the end of September. In 2015 about 240 people participated, including over 100 adults and children with Fabry disease. This year there were about 50 families at the educational conference, and 32 families at camp. This well-organized family event relies upon numerous volunteers to make it a success. Jerry said, "We need about 60 volunteers every year to support our camp. Family and friends, clinic staff, and industry

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staff are welcome and encouraged to apply. It is a great experience! Please submit volunteer applications beginning in July also. You can find more details in the Fabry Family Weekend Camp section near the bottom of the NFDF homepage, and by reading the volunteer application requirements posted on the Victory Junction website at www. victoryjunction.org."

The NFDF also obtains licenses to various peer-reviewed medical publications about Fabry disease, providing free online access to NFDF members. Since the subscription cost of many medical journals is quite high, this free online access for NFDF members to Fabry disease science is a remarkable benefit of NFDF membership. To access publications, register on the NFDF website. According to NFDF's agreement with the publication providers, this is required in order to limit access to the NFDF community only. Anyone in the global Fabry community can register on the NFDF website.

The children at the 2014 camp obliged a delighted Jerry Walters with this group portrait at Victory Junction.

The NFDF actively welcomes international participation of Fabry disease groups and individuals. Jerry said, "We view our Fabry disease community as all individuals with Fabry disease and their family members, as well as our friends, physicians and clinical staff, researchers, care providers, and supporters. The NFDF welcomes and encourages people around the world to sign-up (create an account) on the NFDF website, sign-up for our e-newsletter, and to make use of our programs to the greatest extent possible. We have many programs that may be useful to our international community and we will strive to create more!" The NFDF strongly encourages Fabry patients around the world to become involved in their own country's Fabry patient advocacy groups, to make use of their country's available resources to the fullest possible extent. Of course this does not rule out making use of relevant resources from other countries, such as those provided by the NFDF. Visit: http://www.fabry disease.org/index.php?option=com_k2&view=item&id=270. The NFDF asks, however, that when making charitable donations, please support *your* country's Fabry disease non-profit charitable organizations.

Other programs of the NFDF include its "Faces of Fabry" public-awareness feature on its website; its medical events awareness program; its remembrance program; its Fabry Family Assistance program, a free, confidential, 24/7 service with counselors standing by; its "Urgent and Unmet Needs Fund" for individuals with Fabry on a limited income, for needs not covered by other means; and other programs literally too numerous to mention here. Interested readers will enjoy the highly-detailed downloadable NFDF programs .pdf handout described earlier, as well as the NFDF website, and Facebook page at: www.facebook.com/FabryDisease.

New news and information is usually posted on their Facebook page first. If you would like to see the annual conference and camp in action, take a look at hundreds of photos on the NFDF's Facebook photo

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album entitled "2015 Conference and Camp." Jerry said, "seeing is believing, and believing in 'Longer and Better Lives,' as our motto states, is really important!"

For additional information about the NFDF, please contact Jerry Walter at jerry.walter@fabrydisease.org, or phone 919-932-7785 or 800-651-9131 (U.S. toll free).

Valuable New Feature Premiered at the 2015 National MPS Society Annual Family Conference

By Kendra Gottsleben, M.S., Marketing Communication Specialist at the Center for Disabilities, University of South Dakota; and Rare Disease & Disability Advocate

Each year the National MPS Society hosts a three-day family conference where parents, siblings, caregivers, and individuals who have mucopolysaccharidosis (MPS) or mucolipidosis (ML) come together to learn, educate, connect, and reconnect with others. MPS/ML are such rare diseases that having an organization that is dedicated to keeping families, caregivers, and individuals informed on the latest research findings and assistance programs, as well as providing a place where stories can be shared, is absolutely amazing.

After last year's conference, the National MPS Society Board of Directors decided that an Adult Resource Board needed to be developed; a forum where MPS/ML adults could begin to facilitate with others on the transition into adulthood. In recent years, various treatments have been produced, and as a result, many of us with MPS/ML are living longer lives — presenting many new questions and concerns. The MPS/ML conditions are considered pediatric diseases, so from a research standpoint, we are entering unchartered territory! There is not much data that demonstrates to us what to be looking for as we age with MPS/ML. This is where the Adult Resource Board comes into play.

I have had the honor to be on this board for the last several months with some amazing individuals. It was great to finally meet them in person for the first time in Salt Lake City, UT in September at the 29th annual

Members of the new Adult Resource Board, shown at the 29th Annual National MPS Society Annual Family Conference in September 2015, included, from top row, left: Jason Madison, Nicholas Boyce, Samantha Slawson, Denise Dengel; front row, from left: Jennifer Klein, Madi Thompson, Kendra Gottsleben, Fanny Zambrano. Adult Resource Board Member not pictured: Kali Gegenheimer.

National MPS Society Annual Family Conference. Our session had a wonderful turnout. The questions we received gave us the ability to share our own perspectives on the topics. The only downside was that we needed longer than an hour's time! We could have easily filled several hours, going more in-depth with our presentation. Knowing we were limited to an hour, we kept our focus on the ultimate goal: to have the voices of adults with MPS/ML heard within the greater MPS/ML community and by medical professionals. We shared our personal educational, medical and social obstacles faced throughout our lives. I feel that our Board has great ideas and insights for future conferences and accomplishments, as we move forward.

As I reflect on the past 10 years, the research that has been done has led to MPS/ML lives being fulfilled. The experiences and accomplishments of those of us with

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Valuable New Feature Premiered at the 2015 National MPS Society Annual Family Conference

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Kendra Gottsleben, left, greatly enjoyed sharing good times with her friend Autumn Mortensen at the 2015 National MPS Society Annual Family Conference in Salt Lake City, Utah in September.

rare diseases are astounding. There are college graduates, Master's degrees, employment within large companies, marriages, and families started. Prior to this, the future seemed bleak for many of us. Those of us with MPS/ML have not let our condition define who or what we are. We all keep moving forward and take things as they come. We live life the best we can, and in actuality, that is all any of us can do – whether you have a rare disease or not. Live life, laugh when you can, and always try to use any of life's lemons to make the best lemonade possible!

Don't be shy!

LDNed@umn.edu

The National MPS Society Announces its 2015 Research Grants

The National MPS Society has announced that it allocated $429,500 in grant funding for 2015, which includes the second-year funding for grants awarded in 2014. Thirty letters of intent were recevied by the Society from researchers around the world for the General, MPS I, MPS III and MPS IVA grants. After reviewing those letters, our Scientific Advisory Board review committee requested full grant proposals from ten researchers.

The Board of Directors allocated $94,000 for the first Fundraiser-Directed Research grant. The family who raised these funds requested that they be allocated to Dr. Brian Bigger at the University of Manchester in the UK for his MPS II research, "Improving stem cell therapy for severe MPS II." Learn more about Dr. Bigger and his research at: http://www.human-development.manchester.ac.uk/staff/BrianBigger/.

The Society also generously provided $25,000 to support the Lysosomal Disease Network's NIH contract research goals. The funding is designed for the LDN's Neuroimaging Core, which will benefit its four in-progress MPS projects.

Dr. Michael Gelb at the University of Washington is conducting a pilot study for MPS II newborn screening, and the Society awarded Dr. Gelb $34,000 for this study. For more information about Dr. Gelb, see the August 2015 issue of "**Indications**," page 4.

An additional $16,000 was offered for an ML II/III grant in partnership with ISMRD (International Society for Mannosidosis and Related Diseases). 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 year of the two 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.

The Society also provided $4,500 for post-doctoral Fellows to attend the 2015 Lysosomal Disease Gordon Conference in March.

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The National MPS Society Announces its 2015 Research Grants

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In their 'General Grant' category, the Society chose Dr. Carmine Settembre of the Telethon Institute of Genetics and Medicine of Fondazione Telethon, in Pozzuoli, Italy, for her project entitled "Targeting mTORCI and autophagy pathways to rescue the skeletal phenotype in MPS mouse models."

In their 'MPS I' grant category, the Society chose Dr. Allison R. Kermode, Professor at Simon Fraser University in Burnaby, BC, Canada, for her project entitled "Validation of small molecule therapeutic leads for treatment of MPS I disease."

In the Society's 'MPS III' grant category, they chose Dr. Kim Hemsley of the Lysosomal Diseases Research Unit of the South Australian Health & Medical Research Institute in Adelaide, SA, Australia, for her project entitled "AAV2/8 medicated expression of modified sulphamidase: Liver targeting for improved secretion and brain deliver. Pre-clinical study in the Huntaway dog."

In the Society's 'MPS IVA' grant category, they chose Dr. Ainslie Derrick-Roberts of the Directorate of Genetics & Molecular Pathology, part of SA Pathology, which is the statewide pathology services provider for the public health sector in the state of South Australia, for her project entitled "Creating new tools for understanding skeletal disease in MPS IVA."

For more information about each of these 2015 grants, visit:
http://mpssociety.org/posts/news/2015-research-grants-awarded/.

Batten Disease Support and Research Association (BDSRA) Announces its Newest Research Grant Awards

In 2014, the BDSRA reached out to dozens of researchers to invite Letters of Intent or short proposals to preview work they would like to accomplish in the following year, with a maximum possible grant of $60,000. Once these Letters of Intent were narrowed to requests for full proposals, nearly thirty researchers from universities, children's hospitals, and industry stepped-in to provide peer reviews on a volunteer basis.

The patient advocacy groups Noah's Hope, Drew's Hope, Hope4Bridget, BDSRA-Australia and the Batten Disease Family Association in the United Kingdom have partnered with BDSRA to co-fund the following important projects:

Meaningful Endpoints for Phase III Clinical Trials in Juvenile Batten Disease (CLN3)
Principal Investigator: Heather Adams, Ph.D.
University of Rochester, Rochester, NY $45,000

INCL Gene Therapy Using AAV9 Vectors (CLN1)
Principal Investigator: Steven Gray, Ph.D.
University of North Carolina, Chapel Hill, NC $50,000

Antisense Oligonucleotides for the Treatment of Juvenile Neuronal Ceroid Lipofuscinosis (CLN3)
Principal Investigator: Michelle Hastings, Ph.D.
Rosalind Franklin University of Medicine and Science, North Chicago, IL $50,000

Stop Codon Read-through and Nonsense Suppression for the Treatment of Infantile and Late-Infantile Neuronal Ceroid Lipofuscinosis (CLN2)
Principal Investigator: Michelle Hastings, Ph.D.
Rosalind Franklin University of Medicine and Science, North Chicago, IL $25,000

Astrocytic Thrombospondin-1 in Juvenile Neuronal Ceroid Lipofuscinosis: Impact on Synaptic Dysfunction (CLN3)
Principal Investigator: Tammy Kielian, Ph.D.
University of Nebraska Medical Center, Omaha, NE $50,000

Crossing the Blood Brain Barrier: Enzyme Replacement Therapy for LINCL (CLN2)
Principal Investigator: Peter Lobel, Ph.D.
Rutgers, The State University of New Jersey, Camden, NJ $50,000

NCL Mutation and Patient Database
Principal Investigator: Sara Mole, Ph.D.
University College London, London, United Kingdom, $15,000

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Batten Disease Support and Research Association Announces its Newest Research Grant Awards

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Viral Mediated Gene Therapy in Ovine Batten Disease (CLN5 and CLN6)
Principal Investigator: David Palmer, Ph.D.
Lincoln University, Christchurch, New Zealand,
$50,000

For more information about these grants, visit: http://bdsra.org/2014-research-awards/

Publicly Funded Healthcare in a Quandary

Three children in one family in Saskatoon, Saskatchewan, Canada have been denied provincial coverage of the enzyme elosulfase alfa (commercially marketed as Vimizim™), the only approved enzyme replacement therapy (ERT) for their MPS IVA, a.k.a. Morquio syndrome type A. In early October 2015, Saskatchewan Health Minister Dustin Duncan said that because the children are past the age of five, Vimizim may not even be effective.

Full prescribing information from BioMarin, the manufacturer, states: "Safety and effectiveness of Vimizim have been established in pediatric patients 5 years of age and older. Use of Vimizim in patients 5 years of age and older is supported by an adequate and well-controlled trial in pediatric and adult patients." Full prescribing information can be downloaded at: http://www.vimizim.com/.

Readers may recall reading on page 6 in the August 2015 issue of "**Indications**" that on July 2, 2015, NHS England announced it had declined to fund the cost of Vimizim and referred the matter to a cost-effectiveness analysis by the U.K.'s "National Institute of Health and Care Excellence" (a.k.a. NICE). In Sept. 2015, after further discussions – including the offer of a confidential discount from BioMarin – NICE reversed its decision, issuing a provisional recommendation for Vimizim's adoption by the NHS. A further NHS consultation is now under way, with a final decision expected in January 2016.

Bright Ideas

Check out Kendra Gottsleben and other familiar individuals in a new 27-minute video from BioMarin entitled "The Making of NAGLAZYME" on YouTube: https://www.youtube.com/watch?v=-SsLCQXy4aA

Heavy-Hitting Trio Targets GM1 Gangliosidosis for Gene Therapy

Lysogene (a company in Paris, France) has partnered with Auburn University and University of Massachusetts Medical School and to perform preclinical studies that will provide the groundwork for an Investigational New Drug (IND) application to the FDA for gene therapy for GM1 gangliosidosis. Visit: http://www.lysogene.com/in-the-clinic/gm1gangliosidosis/.

The investigators' approach uses AAV vectors to treat the entire brain and spinal cord after injection of only a

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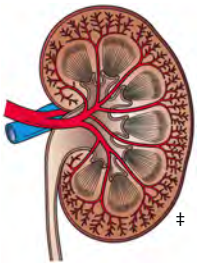
Greetings From the U.K.'s Leukodystrophy Support & Newborn Screening Advocacy Group

"Save Babies Through Screening Foundation UK" is a registered charity founded in 2008 and run entirely by volunteers, including parents and grandparents of children affected by Krabbe leukodystrophy. They are working to advance the health and well-being of children suffering from Krabbe disease and other leukodystrophies in the UK. In addition to supporting families and children affected by leukodystrophies, they are working to promote the extension of the newborn screening program in the United Kingdom for all treatable inherited metabolic disorders. They are very active with legislative and government entities, providing scientific facts and testimony. Learn more about them at: http://www.savebabiesuk.org/about.php. To learn more about Krabbe disease, read the article beginning on page 12 of May 2014 "**Indications**."

LDN Research *Matters*

Podocytes in Fabry Renal Disease



By Evelyn S. Redtree, M.S., S. Michael Mauer, M.D., and Behzad Najafian, M.D.

The current LDN research protocol entitled "Podocytes in Fabry Renal Disease" is a continuation of LDN Protocol # 6702 from the first LDN funding cycle, which was entitled "Natural history and structural functional relationships in Fabry renal diseases." This new project is led by S. Michael Mauer, M.D., as was Protocol # 6702. For additional information about LDN Protocol # 6702, see the February 2014 issue of "**Indications**," on pages 4-5. More information about Dr. Mauer, a University of Minnesota physician, is also found in that issue on pages 7-8.

S. Michael Mauer, M.D.

End-stage renal disease in Fabry disease occurs in more than 50% of males and up to 15% of females.[1] The goals of enzyme replacement therapy for Fabry disease are to reduce suffering and prevent serious end-organ injury that can result in end-stage renal disease, stroke, or serious heart disease.[1-4] Enzyme replacement therapy (replacing α galactosidase A enzyme) has been approved for Fabry disease patients based on clearance within 5 months of the glycosphingolipid globotriaosylceramide (GL-3) from glomerular and peritubular capillary endothelial cells and glomerular mesangial cells.[5] Clearance of GL-3 from arterial smooth muscle cells, distal tubular cells, and especially from podocytes, however, was incomplete even after 11 months of enzyme replacement therapy.[5]

Once kidney disease is clinically manifest with substantial increases in urinary protein, treatment using enzyme replacement therapy frequently cannot stop progression towards kidney failure. Some cells in the kidney's filters (the glomeruli) clear quickly, including endothelial and mesangial cells. The podocytes, located on the outside of the glomerular filter, are crucial for maintaining the filter's barrier to protein leakage into the urine. Loss of podocytes leads to scarring of glomeruli, with resultant loss of filtering function and kidney failure. There are data supporting that earlier initiation of enzyme replacement therapy (ERT) may result in better podocyte GL-3 clearance with ERT. Dr. Mauer hypothesizes that delayed or inadequate treatment (using a low ERT dose) leads to podocyte injury and death, and when podocyte loss becomes critical, to glomerular scarring.

The aims of this research are to: 1) determine the effect of age on podocyte GL-3 content and podocyte numbers in males and females with Fabry disease; 2) study the effects of gender, age at ERT initiation, duration of treatment, and amount of ERT dose on GL-3 clearance from podocytes and other renal cells in children and adults with Fabry disease; 3) evaluate the effects of gender, age at ERT initiation, treatment duration, and amount of ERT dose on podocytes' foot-process width, which is an important indicator of podocyte injury and a correlate of proteinura; and 4) in males with Fabry disease, evaluate the effects of patient age at initiation of ERT on the number of podocytes.

This exhaustive histological research will use the world's largest collection of kidney biopsies, performed before, and at various times after, ERT initiation in adult and pediatric male and female Fabry disease patients. These patients' enzyme replacement therapy has been administered at variable doses, and with variable treatment duration. The investigators have world-class renal morphometry laboratories, and use quantitative electron microscopy measurement tools that they have developed to accurately estimate the kidney structural variables of interest.

The investigators think these studies will strongly contribute to new standards of care regarding age of initial treatment, and dosage of ERT in persons with Fabry disease. They also think their data will help in the design of, and power analyses for, clinical trials of new

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‡ "Kidney Cross Section" Artwork by Holly Fischer, see: http://open.umich.edu/education/med/resources/second-look-series – see the Urinary Tract Lecture, Slide # 6. Licensed under CC BY 3.0, via Commons.

Podocytes in Fabry Renal Disease

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Fabry disease treatments. This is especially true for add-on therapies to ERT, where residual podocyte GL-3 will be the treatment target, since other renal cells will have already cleared with ERT alone.

Behzad Najafian, M.D.

The Co-Investigator of this research protocol is Behzad Najafian, M.D., who is located at the University of Washington in Seattle. Dr. Najafian is an expert renal pathologist with extensive research experience in stereological studies of the kidney, especially in Fabry nephropathy and diabetic nephropathy. Previously, he worked for nearly 10 years with Dr. Mauer at the University of Minnesota before assuming his post at University of Washington. Nonetheless, their collaboration has continued uninterrupted. Dr. Najafian was also Dr. Mauer's collaborator in LDN Protocol # 6702. He has designed several new renal stereological methods for this study.

Podocyturia, a Non-Invasive Predictor of Renal Dysfunction in Fabry Nephropathy

Dr. Najafian is the Principal Investigator of the new LDN Pilot Project I, "Podocyturia, a Non-Invasive Predictor of Renal Dysfunction in Fabry Nephropathy."

Podocytes have limited capacity to regenerate.[6] Podocyte injury and loss leads to both segmental and global glomerulosclerosis,[7,8] common and irreversible lesions in the late states of Fabry nephropathy. Injured podocytes fall into the urine—this is podocyturia. Podocyturia is a robust evidence of podocyte injury with diagnostic and prognostic value in kidney diseases.[9-11] Kidney biopsy studies suggest podocyte injury occurs early and is progressive with increasing patient age in young Fabry disease patients.[11] Dr. Najafian thinks it is likely that podocyturia in Fabry disease precedes and leads to proteinuria, glomerulosclerosis (glomeruli scarring) and reduced glomerular filtration rate (GFR).

Currently, proteinuria and microalbuminuria are used as biomarkers of Fabry nephropathy,[12,13] but these are not sensitive to detect early Fabry nephropathy lesions,[12,14,15] and are even *less* precise renal disease predictors in females with Fabry disease.[16] Moreover, once kidney disease is clinically manifest in Fabry disease, with substantial increases in urinary protein, treatment using enzyme replacement therapy frequently cannot stop progression towards kidney failure. For this reason, Dr. Najafian wants to identify a biomarker to detect early Fabry disease nephropathy in both genders, that can also be used to characterize the patient's Fabry nephropathy risk. This can facilitate correct treatment initiation and ERT dose adjustment. Dr. Najafian is addressing this need by recruiting a cohort of children with Fabry disease. He will study podocyturia in these patients to examine if number of podocytes in urine can predict progression of albuminuria and proteinuria in five years.

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Podocyturia, a Non-Invasive Predictor of Renal Dysfunction in Fabry Nephropathy

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Publications Resulting from LDN Protocol # 6702:

B. Najafian, E. Svarstad, L. Bostad, M.C. Gubler, C. Tøndel, C.B. Whitley, M. Mauer, Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int 79(6) (2011) 663-670. PMCID: PMC3640823.

B. Najafian, M. Mauer, Quantitating glomerular endothelial fenestration: an unbiased stereological approach. Am J Nephrol 33 Suppl. 1 (2011) 34-39. PMCID: PMC3121551.

D.G. Warnock, A. Ortiz, M. Mauer, G.E. Linthorst, J.P. Oliveira, A.L. Serra, L. Maródi, R. Mignani, B. Vujkovac, D. Beitner-Johnson, R. Lemay, A. Cole, E. Svarstad, S. Waldek, D.P. Germain, C. Wanner, Fabry Registry, Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant 27(3) (2012) 1042-1049. PMCID: PMC3289896.

B. Najafian, M. Mauer, R.J. Hopkin, E. Svarstad, Renal complications of Fabry disease in children. Pediatr Nephrol 28(5) (2013) 679-687. PMCID: PMC3811930.

M. Mauer, E. Glynn, E. Svarstad, C. Tøndel, M.C. Gubler, M. West, A. Sokolovskiy, C.B. Whitley, B. Najafian, Mosaicism of podocyte involvement is related to podocyte injury in females with Fabry disease. PLoS One 9(11) (2014) e112188. eCollection 2014. PMCID: PMC4227696.

F.A. Wijburg, B. Bénichou, D.G. Bichet, L.A. Clarke, G. Dostalova, A. Fainboim, A. Fellgiebel, C. Forcelini, K. An Haack, R.J. Hopkin, M. Mauer, B. Najafian, C.R. Scott, S.P. Shankar, B.L. Thurberg, C. Tøndel, A. Tylki-Szymańska, U. Ramaswami, Characterization of early disease status in treatment-naïve male paediatric patients with Fabry disease enrolled in a randomized clinical trial. PLoS One 10(5) (2015) e0124987. eCollection 2015. PMCID: PMC442-5695.

Learn More About Complications of Fabry Disease:

National Fabry Disease Foundation: http://www.fabrydisease.org/. Be sure to read the feature on the homepage entitled "Why Early Diagnosis of Fabry Disease is so Important!" because it strongly pertains to Dr. Mauer's and Dr. Najafian's research.

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Learn More About Complications of Fabry Disease:

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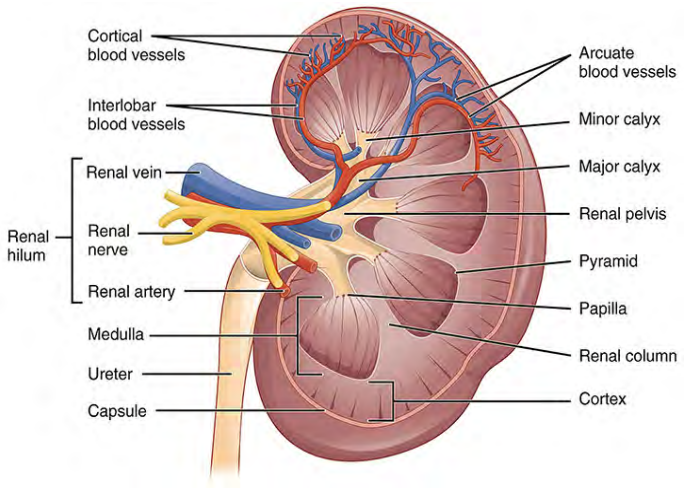
Fabry Support and Information Group: http://www.fabry.org/FSIG.nsf/Pages2/HomePage
A great place to learn more, and to connect with the Fabry disease community: 2016 FSIG Expert Fabry Conference, March 4 – 6, 2016, in San Diego, CA. Registration is $75.00 for the first person, then $25.00 for each additional person over age 10 years. Contact FSIG via their Web site for more information.



National Institute of Neurological Disorders and Stroke (**NINDS**) information about Fabry disease: http://www.ninds.nih.gov/disorders/fabrys/fabrys.htm

NIH Office of Rare Diseases Reseach (**ORDR**) information about Fabry disease: https://rarediseases.info.nih.gov/gard/6400/fabry-disease/resources/1

National Kidney Foundation information about Fabry disease: https://www.kidney.org/atoz/content/fabry

National Organization for Rare Disorders (**NORD**) information about Fabry disease: http://rarediseases.org/rare-diseases/fabry-disease/

From **Emory University School of Medicine**, a downloadable 2-page highly-informative document titled "Fabry Disease: A Guide for the Newly Diagnosed." Visit: genetics.emory.edu/documents/resources/factsheet44.pdf

University of Rostock (Germany), Albrecht Kossel Institute for Neuroregeneration, information about Fabry disease: http://www.sifap.de/3_about_MF/index.php. Be sure to explore the enriched visual resources in the right column of that Web page.

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Julie Eisengart, Ph.D.

Dr. Eisengart published the following, based upon her Fellowship research: J.B. Eisengart, K.D. Rudser, J. Tolar, P.J. Orchard, T. Kivisto, R.S. Ziegler, E.G. Shapiro, Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediat 162(2) (2013) 375-380. PMCID: PMC-3524404. Other presentations that were result of her Fellowship were:

Abstracts:

J.B. Eisengart, K. Bjoraker, E.G. Shapiro, Differences in language functioning in Hurler syndrome before and after HCT: A qualitative comparison of treatments and risk factors. Mol Genet Metab 99(2) (2010) S17.

J.B. Eisengart, K.D. Rudser, A. Ahmed, I. Nestrasil, K. King, R.S. Ziegler, E.G. Shapiro, Differences in attention and executive functioning between MPS types IH, IA, and II: analysis of test performance and quantitative MRI. Mol Genet Metab 102(2) (2011) S17.

J.B. Eisengart, A. Ahmed, K.D. Rudser, I. Nestrasil, M. Potegal, E.G. Shapiro, Positive social functioning in Hurler syndrome: Another brain-based symptom? Mol Genet Metab 102(2) (2011) S17.

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Other presentations:

J.B. Eisengart, A. Ahmed, I. Nestrasil, K.D. Rudser, P.J. Orchard, J. Tolar, R.S. Ziegler, E.G. Shapiro, How subtypes of the mucopolysaccharidoses differentially affect the brain: Neurobehavioral and structural distinctions. Paper presented as part of a symposium on Neuropsychological Functioning in Rare Diseases at the 39th annual meeting of the International Neuropsychological Society in Boston, MA, (2011); Abstract: J Int Neuropsychol Soc 17(S1) (2011) 153.

Dr. Eisengart described her current research focus as "Characterizing both the natural histories and treatment outcomes of several types of the mucopolysaccharidoses." Dr. Eisengart said, "My LDN Fellowship provided me superior training and an excellent foundation not just in understanding MPS and other rare diseases, but also in forming a career in research. Although I wanted to remain in an academic medical center, we moved to Chicago for family reasons. I began as a staff neuropsychologist within a major health system there, doing clinically-focused work. When the opportunity arose to return to Minnesota, I was quite pleased to take the position of Assistant Professor and continue being a part of the wonderful work on lysosomal disease research at the University of Minnesota."

Jeanine R. Jarnes Utz, PharmD

Jeanine R. Jarnes Utz, PharmD, also an LDN Fellow during 2009-2010, was mentored by James C. Cloyd, PharmD at the University of Minnesota. Dr. Utz currently serves as pharmacotherapy provider at the Advanced Therapies Clinic, University of Minnesota, Fairview. She is also Adjunct Assistant Professor in the Experimental and Clinical Pharmacology Department at the University of Minnesota College of Pharmacy. She is also Director of the "Pharmacotherapy of Inherited Metabolic Diseases" post-doctoral PharmD Fellowship training program through the College of Pharmacy, and mentor of the LDN Fellow who shares in that Fellowship from the College of Pharmacy, at the University of Minnesota.

Her Fellowship research projects were entitled "The Natural History of the Gangliosidoses" and "Biomarkers of Central Nervous System Inflammation in Infantile and Juvenile Gangliosidoses." So far, the publication that resulted from these research projects is:

J.R. Utz, T. Crutcher, J. Schneider, P.J. Sorgen, C.B. Whitley, Biomarkers of Central Nervous System Inflammation in Infantile and Juvenile Gangliosidoses. Mol Genet Metab 114(2) (2015) 274-280. PMCID: PMC438-6860.

Dr. Utz presented this platform presentation at WORLD*Symposium* 2014:

J.R. Utz, P. Sorgen, T. Crutcher, C.B. Whitley, Metabolomic study of CSF and serum markers in infantile and juvenile gangliosidosis diseases. Mol Genet Metab 111(2) (2014) S107.

Dr. Utz presented this poster at WORLD*Symposium* 2015:

J. Utz, T. Crutcher, J. Schneider, C.B. Whitley, Biomarkers of central nervous system inflammation in infantile and juvenile gangliosidoses. Mol Genet Metab 114(2) (2015) S118-S119.

Dr. Utz's current research focus is the natural history of, and development of treatment for the gangliosidosis diseases. She said, "Participation as an LDN Fellow was a tremendous learning experience and was influential in helping me decide upon my research interests going forward."

Also during 2010, Moin Vera, M.D., Ph.D. was mentored in his LDN Fellowship by Patricia I. Dickson, M.D. at Harbor-UCLA Medical Center. Dr. Vera's Fellowship research project was entitled "The Immune Response to Intrathecal Enzyme Replacement Therapy in Mucopolysaccharidosis I Patients." Dr. Vera subsequently published the following, based upon his Fellowship

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research: M. Vera, L. Le, S.H. Kan, H. Garban, D. Naylor, A. Mlikotic, I. Kaitila, P. Harmatz, A. Chen, P.I. Dickson, Immune response to intrathecal enzyme replacement therapy in mucopolysaccharidosis I patients. Pediatr Res 74(6) (2013):712-720. PMID: 24002329.

Moin Vera, M.D., Ph.D.

Since completing the LDN Fellowship, Dr. Vera completed fellowship training in clinical genetics and medical biochemical genetics at the UCLA Intercampus Medical Genetics Training Program. He then joined the faculty in the Department of Pediatrics, Division of Medical Genetics, at the Harbor-UCLA Medical Center in Torrance, CA. Currently Dr. Vera is Health Sciences Assistant Clinical Professor, Step II, in the David Geffen School of Medicine at UCLA, Department of Pediatrics, Division of Medical Genetics, Harbor-UCLA Medical Center. His research is focused on inflammation and immune dysfunction in inborn errors of metabolism, such as the mucopolysaccharidoses. Dr. Vera said, "The LDN Fellowship provided the funding necessary for me to complete the research project, leading to a significant publication which has been a direct contributor to my gaining my current position."

During her 2010-2011 LDN Fellowship, Sarah Lo, M.D. then of the Section of Hematology-Oncology, Department of Pediatrics, Yale University School of Medicine, was mentored by Pramod Mistry, M.D., Ph.D. at Yale University. Dr. Lo is now at Children's Hospital of Philadelphia, serving as Attending Physician/Hospitalist, Blood and Marrow Transplant Program. Her research project resulted in the following publication: S.M. Lo, J. Liu, F. Chen, G.M. Pastores, J. Knowles, M. Boxer, P.K. Mistry, Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. J Inherit Metab Dis 34(3) (2011) 643-650. PMCID: PMC3782382. This article is freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3782382/.

Wenyong Tong, Ph.D.

Wenyong Tong, Ph.D. (McGill University) was an LDN Fellow during 2012. From 2012 to 2015, as a post-doctoral fellow, he studied MPS diseases at University of California San Diego School of Medicine, in the Glycobiology and Research Center and Dept. of Cellular and Molecular Medicine. Dr. Tong was mentored there by Jeffrey Esko, Ph.D. Dr. Tong's LDN Fellowship research project was entitled "Novel Transporters for MPS I Enzyme Replacement Therapy." As a result of his LDN Fellowship research project, Dr. Tong published one paper: M. Inoue, W. Tong, J.D. Esko, Y. Tor, Aggregation-mediated macromolecular uptake by a molecular transporter. ACS Chem Biol 8(7) (2013) 1383-1388. He also gave a poster presentation in the 3rd "Conference on Clinical Research for Rare Diseases" (CCRRD) in October 2012 in Rockville, Maryland. He subsequently published the following abstract, based upon his Fellowship research project: W. Tong, S. Sarrazin, Y. Tor, J.D. Esko, Novel transporters for MPS I and MPS IIIA enzyme replacement therapy. Mol Genet Metab 108(2) (2013) S92. In 2014 Dr. Tong also presented this research as a poster at the "Experimental Biology" meeting in San Diego. (For more information about this meeting, visit: http://experimentalbiology.org/2016/Home.aspx).

Dr. Tong's interest in lysosomal diseases has continued. He has developed one US patent: Intranasal adminis-

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tration of guanidinylated aminoglycosides (WO201-4159878 A2, 2014), J.D. Esko, Y. Tor, W.Tong. In February 2015 he was co-author of two abstracts presented at the WORLD*Symposium*: (1) J. Esko, W. Tong, K. Hamil, Y. Tor, Intranasal enzyme replacement therapy in mice. Mol Genet Metab 114(2) (2015) S42-S43, which Dr. Tong presented on the platform; and (2) R.Y. Wang, P.L.S.M. Gordts, W.C. Lamanna, S. Sarrazin, J.C. Gonzales, S. Kan, W. Tong, P.I. Dickson, J.D. Esko, The mucopolysaccharidosis type IIIA murine model demonstrates increased brown adipose activity and energy demand, resulting in postprandial hypertriglyceridemia. Mol Genet Metab 114(2) (2015) S125.

Dr. Tong said, "My research field is in pharmacology and glycobiology. The LDN Fellowship provided me the excellent opportunity to study glycan-related diseases such as mucopolysaccharidosis (MPS) and develop a general technology for delivery of therapeutic biologicals to the brain. With this Fellowship support, I obtained great training on drug discovery for glycan-related diseases at the Glycobiology Research and Training Center of the University of California, San Diego (UCSD). I would like to dedicate my career to drug discovery and research development in glycan-related disease and working to uncover drug pathways for unmet medical needs like brain disorders." As a research associate, Dr. Tong is now working at the Scripps Research Institute in La Jolla, California.

Alia Ahmed, M.D., CCRP

During 2012-2013, Alia Ahmed, MD, CCRP, was an LDN Fellow at the University of Minnesota and was mentored by Elsa Shapiro, Ph.D. Her Fellowship research project sought to evaluate the phenotype and genotype relationship in mucopolysaccharidosis type I. Like Dr. Tong, Dr. Ahmed presented her research at the Conference on Clinical Research for Rare Diseases in Rockville, Maryland in October 2012. She presented her research as a poster at the 9th annual WORLD*Symposium*, February 2013, in Orlando, Florida; this was published as: A. Ahmed, R. Cooksley, K.D. Rudser, C.B. Whitley, E.G. Shapiro, Relationship of genotype, treatment and age with medical phenotype in mucopolysaccharidosis type I. Mol Genet Metab 108(2) S17-S18.

Dr. Ahmed also presented her Fellowship research in a poster at the 63rd annual meeting of the American Society of Human Genetics in October 2013 in Boston, Massachusetts.

Dr. Ahmed's research resulted in this article: 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 α-L-iduronidase gene in Hurler-Scheie syndrome. Mol Genet Metab 111(2) (2014) 123-127. PMCID: PMC3939822.

Dr. Ahmed is currently serving as a Research Associate in the Department of Pediatrics at the University of Minnesota. Dr. Ahmed said, "Thanks to performing this Fellowship, I have developed my knowledge of rare diseases. I would like to suggest at the end of training to provide/arrange for a certificate mentioning/reciting some detail about the training."

Zoheb Kazi, MBBS

Zoheb Kazi, MBBS, of Duke University, was an LDN Fellow during 2013-2014, and was mentored by Dr. Priya Kishnani. Dr. Kazi's Fellowship research project was entitled "An "omics" approach to the identification of factors influencing immune response to ERT in Pompe disease." In pursuit of this research project Dr. Kazi used: 1) whole exome sequencing; 2) human leukocyte antigen (HLA) typing; 3) comprehensive immune phenotyping; and 4) differential expression proteomics in patients with Pompe disease who have demonstrated atypical/unexpected antibody respon-

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ses, as well as those with typical/expected antibody responses to enzyme replacement treatment (ERT) with recombinant human acid α-glucosidase (rh-GAA; alglucosidase alfa). The purpose of his research was to predict, prior to the initiation of ERT, which patients are at risk for developing high antibody titers. An "omics" approach aimed to identify modifier genes and proteomic signature profile, as well as to gain a greater understanding of factors influencing immune response (HLA type and other immunologic factors), to identify the patients likely to mount an immune response to ERT. This information can help guide optimal implementation of immune tolerance-inducing agents, resulting in improved therapeutic outcomes and maximal long-term benefits for these patients. So far, this publication has resulted from Dr. Kazi's research: E.O. Stenger, Z. Kazi, E. Lisi, M.J. Gambello, P. Kishnani, Immune tolerance strategies in siblings with infantile Pompe disease – advantages for a preemptive approach to high-sustained antibody titers. Mol Genet Metab Rep 4 (2015) 30-34. PMCID: PMC4497810 [Available on 9-1-2016].

Currently, Dr. Kazi remains involved in research on Pompe disease at Duke University, exploring immunogenicity of therapeutic proteins in Pompe disease. He hopes to obtain a pediatric–medical genetics residency, to further his goal of becoming a research physician. Dr. Kazi said, "My LDN Fellowship allowed me to perform an in-depth analysis of the current issue at hand – immunogenicity of therapeutic protein in Pompe disease, utilizing a proteomics approach. My LDN Fellowship has also been extremely helpful in strengthening my profile for my medical residency application."

Kelly King, Ph.D. was an LDN Fellow during 2013-2014 at the University of Minnesota. She was mentored by Elsa G. Shapiro, Ph.D. Her Fellowship research project was entitled "Attention and Corpus Callosum Volumes in Individuals with Mucopolysaccharidosis Type I."

Kelly King, Ph.D.

Since completing her LDN Fellowship, Dr. King has continued as a licensed psychologist and an Assistant Professor in the Dept. of Pediatrics at the University of Minnesota. She also continues to play a key role as a sub-investigator in the ground-breaking LDN study, Protocol # 6703, entitled "Longitudinal studies of brain structure and function in MPS disorders," as well as being involved in other ongoing LDN studies at the University of Minnesota. Dr. King said, "I am thankful for the LDN fellowship as it allowed me to continue my work with individuals and families affected by MPS, and meet and collaborate with others passionate about lysosomal disease research."

So far, the following presentations have resulted from her LDN Fellowship research project. Her Fellowship research based manuscript is still in progress, and will be submitted to a peer-reviewed medical journal.

Poster:

E.G. Shapiro, K. King, K. Delaney, A. Ahmed, B. Yund, K. D. Rudser, C.B. Whitley, Factors affecting psychological adjustment in MPS I patients: an exploratory study and clinical observations. Presented at 10th annual Lysosomal Disease Network WORLD*Symposium*, February 11-13, 2014, San Diego, California. Abstract: Mol Genet Metab 111(2) (2014) S95.

Poster and Platform Presentation:

K. King, K.D. Rudser, V. Kovac, I. Nestrasil, B. Yund, K. Delaney, J. Wozniak, B. Mueller, K. Lim, M. De Bellis, E.G. Shapiro, Attention and corpus callosum volumes in individuals with Hurler and Hurler-Scheie syndromes and controls. Presented at 10th annual Lysosomal Disease Network WORLD*Symposium*, February 11-13, 2014, San Diego, California. Abstract: Mol Genet Metab 111(2) (2014) S60-S61.

Mari Mori, M.D., of Duke University, an LDN Fellow during 2014-2015, has a unique background, having formal training in both medical genetics and in bioinfor-

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matics. She was also awarded a 2015 Pfizer/American College of Medical Genetics and Genomics Foundation "Clinical Genetics Combined Residency for Translational Genomic Scholars" scholarship, to perform research on phenotype modifiers of Pompe disease. Her LDN research project was entitled "Identification of modifier genes of Pompe disease phenotype by analysis of whole exome sequencing (WES) data." Dr. Mori is still compiling and analyzing her extensive data resulting from her LDN research. Peer-reviewed publication of her research findings will occur in the future.

Mari Mori, Ph.D.

Dr. Mori will explore potential modifier genes that alter the severity and onset of Pompe disease phenotype with different organ involvement. Dr. Mori will also analyze potential genetic modifiers of immune response to enzyme replacement therapy (ERT) in patients with Pompe disease. Patients predicted to develop antibodies against ERT would benefit from immunomodulation prior to the start of ERT. Her LDN project expands the Pompe disease WES data at Duke University, which represents a very large dataset and provides a unique opportunity for learning about the disease.

Dr. Mori said, "Prediction of onset and disease severity is critical in determining the optimal therapy especially for asymptomatic patients who can be detected by newborn screening (NBS). NBS for the disease is likely to be available in more states in the future, as Pompe disease has been added to the federal Recommended Uniform Screening Panel this year. I hope identification of modifying genetic factors may lead to more personalization of enzyme replacement therapy and potential for identifying new therapeutic targets. I am deeply grateful to LDN and my mentor Dr. Priya Kishnani for giving me this unique opportunity to participate in the translational part of patient care."

Joseph Schneider's University of Minnesota-based LDN Fellowship during 2014-2015 was combined with the "Pharmacotherapy of Inherited Metabolic Diseases" (PIMD) Fellowship from the University of Minnesota College of Pharmacy. His mentor in both of these Fellowships was Jeanine R. Utz, PharmD. His research project for both of these Fellowships was entitled "Hypothyroidism in Adult Onset Pompe Disease." Dr. Schneider's publication from his research is currently in process.

Joseph Schneider, PharmD

After completing his Fellowships on June 30, 2015, Dr. Schneider became Shire's upper-midwest Senior Rare Disease Medical Science Liaison. Dr. Schneider said, "The LDN and PIMD Fellowships have exposed me to the complex care and needs of patients with lysosomal diseases. The fellowships also provided an opportunity to be a part of the research process in rare diseases, and to understand the challenges in performing research within rare diseases. This in-depth exposure has proved to be essential in my new professional focus working within Medical Affairs in rare diseases. Furthermore, I would like to thank the NIH for funding the LDN, and thank Genzyme for funding the PIMD Fellowship. These Fellowships provided me with great opportunities, and helped direct my professional career in the biopharmaceutical industry."

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Zahra Karimian, PharmD, is a 2015-2016 LDN Fellow at the University of Minnesota. She is supported by two fellowships: the LDN, and the University of Minnesota College of Pharmacy's "Pharmacotherapy of Inherited Metabolic Disorders (PIMD)" Fellowship. Her mentor in these Fellowships is Jeanine R. Jarnes Utz, PharmD, who is the Principal Investigator of LDN Protocols # 6713 and 6729. Dr. Karimian's LDN Fellowship research project is entitled "Classification and Management of Infusion Reactions to Enzyme Replacement Therapy (ERT) in Lysosomal Diseases (LD)." This project addresses therapeutic management of a serious problem affecting lysosomal disease patients who receive ERT — namely, serious adverse reactions to the proteins contained in replacement enzymes. Although her research project has just begun, she will have an abstract reflecting her research findings at the 2016 WORLD*Symposium* in San Diego.

Dr. Karimian has been studying pharmacy at the University of Minnesota. She said, "After graduating from the College of Pharmacy at the University of Minnesota, I went abroad and served as a pharmacist in a mobile clinic which was funded by several international and national non-profit organizations in the Middle East. I also worked at the Clinical Trials Department of the FDA in Iran, which gave me a better understanding of clinical research from a regulatory perspective." Regarding future plans, Dr. Karimian said, "I really enjoy working in an academic setting, where I can teach and do research, but I'm always interested in exploring other areas in the field of pharmacy."

Melani Solomon, Ph.D. is a 2015-2016 LDN Fellow who is performing research at the Institute of Bioscience and Biotechnology Research at the University of Maryland as a postdoctoral associate. Her mentor is Silvia Muro, Ph.D., Associate Professor of Bioengineering and affiliate faculty in Cell Biology and Molecular Genetics at that Institute, which is located in College Park, Maryland.

Melani Solomon, Ph.D.

As a graduate student at Massachusetts College of Pharmacy and Health Sciences in Boston, Dr. Solomon focused her efforts on generating three-dimensional tumor spheroids and studying the distribution of drugs and drug delivery systems in this model. Her masters thesis exploited pharmacokinetic tools to model the kinetics of distribution of small molecules in the spheroid model. During her doctoral training, she further explored the spheroid model to test the efficacy of high-throughput nanocarrier-based drug delivery systems. In so doing, she used assays that are normally performed in monolayer cultures, adapting them to the spheroid system. Realizing the potential of this model as a more realistic in vitro tumor model, and to characterize the properties of their three-dimensional surface, she worked with a collaborating lab in performing atomic force microscopy experiments on spheroids, an avenue which had not been previously explored.

As a graduate student, Dr. Solomon was also involved in some other drug delivery projects that dealt with the design and testing of mitochondriotropic ligands for sub-cellular targeting of bioactives. Through this project, she demonstrated that delivering drugs specifically to their sub-cellular target could sensitize resistant cells to treatment. She was also part of a team that synthesized less toxic ligands for mitochondrial targeting, which will serve as an effective delivery system for therapeutics where toxicity is the limiting factor.

During her postdoctoral fellowship at Johns Hopkins University in Baltimore, Dr. Solomon trained in a

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LDN Fellowships Have Wide-Ranging Positive Effects

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laboratory that is focused on screening small molecules for lysosomal diseases, allowing her to gain experience in establishing clinically-relevant models to screen small molecule therapies for Krabbe disease. She has also established a technique to analyze the sphingolipid profiles in brains of patients with different lysosomal diseases, and identified a common underlying mechanism that might be responsible for the pathology of these disorders.

Dr. Solomon's LDN Fellowship research project is entitled "Evaluation of transcytosis mechanisms in lysosomal storage disease brains." This research project has three specific aims: 1. to study the classical endocytic mechanisms in endothelial cells lining the brain microvasculature in patients with different lysosomal diseases; 2. to assess the expression of markers of the classical endocytic pathways and the non-classical CAM pathway of brain endothelial cells of patients with different lysosomal diseases; and 3. to prepare nanocarriers whose surface will be modified with antibodies against the different endocytosis receptors, and to assess their differential uptake and transcytosis across in vitro blood-brain barrier models.

Postmortem brain tissues from patients with the following lysosomal diseases will be examined in this study: Fabry, Niemann Pick type C, Pompe, Krabbe, metachromatic leukodystrophy, Gaucher, Tay-Sachs, GM1-gangliosidosis, and multiple sufatase deficiency. The classical endocytic mechanisms of clathrin-mediated endocytosis (CME) and caveolae-mediated endocytosis (CavME), as well the non-classical cell adhesion molecule (CAM)-mediated pathway, will be studied by immunoelectron microscopy techniques. Using transmission electron microscopy, the expression of their respective markers transferrin, GM1 ganglioside and intercellular cell adhesion molecule (ICAM-1) will be evaluated. These findings will be confirmed by immunohistochemistry of brain sections, as well as western blotting of extracted proteins to identify and quantify proteins associated with these endocytic pathways. Finally, polystyrene nanoparticles surface-coated with ICAM-1 antibody, transferrin, or cholera toxin B will be prepared to target the CAM, CME and CavME pathways respectively. These nanoparticles will be tested for their transcytosis across the blood-brain barrier using an in vitro blood-brain barrier model.

It is Dr. Solomon's hope that this data will serve to revolutionize the field of enzyme replacement therapy for the lysosomes by providing: (1) a mechanistic understanding of the pathways common to several lysosomal diseases that can be exploited to transcytose the blood-brain barrier; and (2) a potential treatment approach that can be easily tailored for each lysosomal disease by substituting the enzyme on the ICAM-1 targeted nanocarrier.

Dr. Solomon said, "In my free time I like to read (especially works of scientific fiction), travel and cook. I find adventure sports extremely invigorating. My newfound joy, though, is in being a mother. I have a 7-month-old son and he's been the center of my world ever since he came into this world! I firmly believe that it is important to maintain a work-life balance, and I have been able to achieve my goals as a scientist and a mother so far. While parents are generally proud of their children, I hope my son will be proud of me one day."

Graduate students and post-doc researchers who might possibly be interested in applying for a future LDN Fellowship are encouraged to sign-up to the LDN e-mailing list. This can easily be done by sending a request to: LDNed@umn.edu. Once each year, a request for LDN Fellowship applications is sent to the entire LDN e-mailing list.

Persons with Attenuated MPS I Needed for New Clinical Trial

Visit: http://www.breakingbarriersmpsitrial.com/

AGT-181, α-L-iduronidase fusion protein, is an investigational enzyme replacement therapy (ERT) from ArmaGen, Inc. designed to treat symptoms and complications of Hurler syndrome both in the body (somatic) and the central nervous system (consisting of the

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NPC1 Clinical Trial is Seeking NPC1 Patients for Enrollment

Vtesse, Inc., a recently-created rare disease pharmaceutical company, has announced its new clinical trial called the "NPC Study." This is a Phase 2b/3 randomized, sham-controlled clinical trial designed to evaluate the efficacy and safety of VTS-270. The primary objective of the NPC Study is to evaluate the progression of the neurologic manifestations of Niemann-Pick disease type C1 (NPC1) in children treated with VTS-270, as compared to those who do not receive the drug.

Forbes D. Porter, M.D., Ph.D.

VTS-270 is a proprietary formulation of 2-hydroxypropyl-β-cyclodextrin (a.k.a. HP-β-CD) for the treatment of children with Niemann-Pick disease type C1. VTS-270 has been evaluated in preclinical and clinical studies at institutes within the National Institutes of Health (NIH) to treat patients with NPC1. Dr. Forbes Porter was the Principal Investigator for the Phase I clinical trial of VTS-270 at NIH. Dr. Porter serves as the Clinical Director for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). He is also Senior Investigator and Program Head in the intramural research program of the Developmental Endocrinology and Genetics Program (PDEGEN) at NICHD. He is Co-Principal Investigator of this Phase 2b/3 study, and a member of the scientific advisory committee for Vtesse, Inc. Dr. Porter said, "The VTS-270 pivotal study addresses a pressing need to discover new treatments for the disease."

Vtesse is actively recruiting patients for the trial. They are planning on opening up to 20 sites in the U.S. and Europe. More information about enrolling in the NPC Study can be found at: http://www.thenpcstudy.com/#!about-the-npc-study/c1wiq. Find this clinical trial on ClinicalTrials.gov under the identifier number NCT02534844. If you would like to contact Vtesse directly, please contact Carrie Burke at: carrie@vtessepharma.com or 240-801-9268.

The NPC Study is open to children ages 6-21 who have been diagnosed with NPC1 and meet all the entry requirements. Two-thirds of the participants will receive VTS-270 through intrathecal (IT) administration, via a lumbar puncture; the other third will undergo a sham procedure (a needle prick that does not penetrate beyond the skin), both of which will be given under either general anesthesia or conscious sedation. Use of either general anesthesia or conscious sedation will be based upon an individual study site's standard practice.

After 12 months of bi-weekly injections or sham control procedures, all participants — including those randomized to sham control procedures — will be eligible to receive VTS-270 in the open-label extension phase of the trial, until the regulatory agencies make a decision whether or not to approve VTS-270. In addition, any participants in the sham group who show significant disease progression will be removed from the sham group and placed in the open-label part of the trial, where they are guaranteed to receive VTS-270.

To learn the in-depth background of HP-β-CD, read "Collaborative development of 2-hydroxypropyl-β-cyclodextrin for the treatment of Niemann-Pick type C1 disease," an article published in the journal *Current Topics in Medicinal Chemistry* in 2014; PMCID: PMC4048128. This article is freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4048128/.

ArmaGen, Inc. Clinical Trial

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brain and spinal cord). The purpose of the Phase I trial is to determine a safe and well-tolerated dose of AGT-181 in adults with attenuated MPS I (Scheie or Hurler-Scheie syndrome). AGT-181 is designed to cross the blood-brain barrier in the same way insulin does.

Patients in the trial will receive weekly infusions of AGT-181 at assigned doses that range from 1 mg/kg for the first dose-group of patients enrolled, and increase to 3.0 mg/kg. Additional higher dose levels may be added.

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Sanfilippo Syndrome type D Global Patient-Search Underway

Jill Wood of **Jonah's Just Begun** (http://jonahsjustbegun.org/) has advised the LDN that for the last year, Phoenix Nest (http://www.phoenixnestbiotech.com/) has been working with Dr. Patricia Dickson and colleagues at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center to develop an enzyme replacement treatment (ERT) for MPS IIID (Sanfilippo syndrome type D). Their strategy proposes to deliver the recombinant human α-N-acetylglucosamine-6-sulfatase (rhGNS) enzyme intrathecally (into the spinal fluid) in order to effectively treat the brain.

Barbara Wedehase, MSW, CGC, Executive Director of the National MPS Society (left) and Dr. Patricia Dickson of Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center at WORLD*Symnposium 2013 in Orlando.*

Jill said, "We are in the process of writing a grant proposal to study this ERT in the mouse model. After that, it will be on to larger animal studies, before getting FDA approval to go into the clinic. But we need to find MPS IIID patients to get their support to make our case to the NIH, and potentially to any one that would fund this work." MPS IIID is an extremely rare disease, and it is difficult to enroll adequate numbers of these patients for possible inclusion in a future clinical trial. Jill continued, "We would appreciate the efforts of anyone who can help bring MPS IIID patients to our attention, or at the very least, get them to sign up in the Sanfilippo patient registry (https://connect.patientcrossroads.org/?org=SanfilippoRegistry). We need these families to know that Phoenix Nest, as a patient-family driven company, is working on a treatment. We may be several years away from the clinic, but we have a team dedicated to this project. So please spread the word, and help us find the families that are dealing with MPS IIID." Their patient search encompasses the entire world. A glance at the "Partner Organizations" shown on the above-mentioned Sanfilippo Registry page is a fascinating *Who's Who* of humanity's Sanfilippo syndrome patient advocacy organizations. Please join the effort to identify and contact every MPS IIID individual in the world!

ArmaGen, Inc. Clinical Trial

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AGT-181 will be administered intravenously over a 3-4 hour period for eight weeks. Following treatment, investigators will collect a sample of cerebrospinal fluid through a minimally-invasive diagnostic test. This fluid will be tested to confirm whether there is a reduction in levels of participant's glycosaminoglycans.

Some key criteria for participation in this study are:

- Patients age 18 years or older diagnosed with attenuated MPS I (Hurler-Scheie or Scheie syndromes);
- Must provide voluntary written consent;
- Patients on current enzyme replacement therapy (ERT) must discontinue ERT for at least 6 weeks before and during the duration of the trial.

For extensive details about this study, find this study on ClinicalTrials.gov (visit: https://clinicaltrials.gov/ct2/search/index) using the identifier number NCT0237-1226.

Study sites will include the following, after institutional ethics board approvals: University of Minnesota in Minneapolis, Minnesota; and investigators in Orange County, California; Salt Lake City, Utah; and Chicago, IL. Approvals at these sites are pending.

There are two active study sites so far: Emory Lysomal Storage Disease Center, Emory University; and Children's Hospital of Pittsburgh of UPMC.

Heavy-Hitting Trio Targets GM1 Gangliosidosis for Gene Therapy

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few intracranial sites. Their work will involve studying GM1 gangliosidosis mouse and cat models, and new injection routes, to determine the optimal approach to be translated in human patients. Lysogene plans a phase I/II trial of gene therapy in GM1 gangliosidosis, with an anticipated start-date of 2017.

Calendar of Upcoming Events

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

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

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

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

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

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

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

The Penn Medicine Orphan Disease Center (ODC) will host the 3rd Annual Million Dollar Bike Ride on Saturday, May 7th, 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.milliondollarbikeride.org/ or contact Samantha Charleston at: scharle@upenn.edu or phone (215) 573-6822.

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

The 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 this issue about the National Fabry Disease Foundation for detailed information, and visit: http://www.fabrydisease.org/

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

New Clinical Trial of ERT for Niemann-Pick Disease Type B

Genzyme, a Sanofi Company, has launched a Niemann-Pick disease type B Phase I/II pediatric clinical trial, known by its shortened name as "ASCEND-Peds." Extensive details about this trial are available at ClinicalTrials.gov by searching for its identifier number NCT02292654 at: https://clinicaltrials.gov/ct2/search/index. The primary objective of this clinical trial is to evaluate the safety and tolerability of olipudase alfa (acid sphingomyelinase) administered as an intravenous infusion every 2 weeks for 52 weeks. The clinical trial site for the U.S. is Mount Sinai Hospital in New York City, under the direction of Dr. Melissa Wasserstein. This site is now actively recruiting pediatric patients for this clinical trial.

Indications™

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Keys to Understanding the Lysosomal Disease Network

Lysosomal Disease Network