
# International Conference for Glycoprotein Storage Diseases

**28th - 29th July 2012**



**Charleston, South Carolina, United States**

## Program & Abstracts

Greenwood Genetic Center

ISMRD

# International Conference for **Glycoprotein Storage Diseases 2012**

Support for the scientific meeting has been provided by the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R13NS080489, Principal Investigator S. Cathey.

# A very special thank you

**ISMRD would like to thank the following organizations and companies for their very generous support.**

EVERYLIFE FOUNDATION FOR RARE DISEASES

Mercy Medical Airlift

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## A very special thank you to the following organizations and people who have supplied quilts, drink bottles, art sets, and itune gift cards for the children's and affected adults' program.

- Linus Project – Charleston for making quilts for our affected patients and their siblings.
- Sharon Vincent for donating the water bottles.
- Artmart St Louis for donating water color art sets. **www.artmartstl.com**
- Paula Myteck for donating iTune gift cards.
- CBIZ for donating money to purchase iTune gift cards.
- Build a Bear for donating bears. **www.buildabear.com**

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## Conference Committee:

Sara Cathey
Jenny Noble
Mark Stark
Pam Tobey
Susan Kester
Jackie James
Andrea Gates
John Forman
Melissa Rust
Carolyn Paisley-Dew
Steve Walkley
Mark Haskins
Marc Patterson
Thomas Braulke
Tim Wood
Laura Pollard
Richard Steet

## ISMRD Contact Information:

Website: www.ismrd.org
Email: info@ismrd.org

# Welcome

On behalf of the Greenwood Genetic Center, welcome to South Carolina. The Greenwood Genetic Center (GGC) is privileged to be the host institution for the Third International Workshop on Glycoproteinoses. The collaborative relationship between GGC and ISMRD began in 2005 and led to Mucolipidosis Clinics at the Center's main campus in Greenwood, SC in 2006 and 2009. Ongoing partnership led to inclusion of the glycoproteinoses in the NIH's Rare Diseases Clinical Research Consortium focused on lysosomal diseases. This workshop brings together patients and families affected by any of the glycoprotein storage disorders, clinicians who care for these patients, and researchers who study the diseases.

While the ultimate goal is effective therapies for these disorders, the planning committee for the workshop began with four key questions:

1. How can patients and families become more connected and involved in research?
2. How can collaborations be fostered among the laboratory and clinical scientists actively studying the glycoproteinoses?
3. How can the glycoproteinoses community benefit from progress made in other lysosomal diseases (for example: enzyme replacement therapy, chaperone therapy, newborn screening, biomarker analysis)?
4. How can longitudinal studies be promoted and accessible to patients and families?

It was determined that three events were needed - a scientific meeting, a family meeting, and specific longitudinal study clinics. To maximize the impact of each of the three components, the events have been combined into this special weekend. Families and researchers have travelled from around the world to participate. Charleston is a city rich in history. Thank you for joining us here for this historic event for the glycoproteinoses.

Sara Cathey, M.D.
Greenwood Genetic Center

# Welcome

As President of ISRMD, I would like to welcome researchers and families to our joint Scientific and Family Conference for Glycoprotein Storage Diseases. The mission of ISMRD is to be the leading advocate for families worldwide affected by glycoprotein and related storage diseases. Through partnerships built with medicine, science and industry, we seek to detect and cure these diseases, and to provide a network of support and information.

Our vision is a future in which children with glycoprotein and related storage diseases can be detected early, treated effectively, and go on to live long, healthy and productive lives; a future where doctors and other clinicians are knowledgeable of and able to detect these genetic defects efficiently and with accuracy.

This conference is a very important part of ISMRD's mission; it brings together researchers from all over the world to share new data and understanding of the diseases, it allows families of affected people to share experiences and learn from each other, and it provides the unique opportunity for families to meet researchers and physicians studying these diseases. This is our third such conference; it would not be possible to bring all of you together without the generous contributions of our sponsors, our families, and of the National Institutes of Health. I would like to invite all of you to participate and enjoy the agenda, to renew old acquaintances, and to meet new friends that share our common goal of a cure for these terrible diseases. I also believe this is a great opportunity for you to learn more about ISRMD and its mission, and I trust you will continue to support us and will participate in helping families affected by glycoprotein diseases.

I would like to add a special thank you to Dr. Sara Cathey and the Greenwood Genetic Center. Dr. Cathey and her team are doing an amazing job to pull together a family conference, a family history study, and a scientific conference in the same weekend. Dr. Cathey was also the researcher who was able to obtain the conference grant from the NINDS. Without her tremendous energy, we would not be able to put this event together.

Mark Stark
President, ISMRD

# ISMRD | Mission & Governance

ISMRD is a U.S. 501 (c)3 charity that is governed by an all-volunteer organization led by a Board of Directors whose backgrounds span nations, diseases and experience. Each member of the Board serves a two-year term, which can be renewed upon the approval of the remaining members. We actively seek out others whose experience and background enhance our ability to carry out our Mission, and whose passion for that Mission enables us to reach our goals.

We seek a future in which children with Glycoprotein & Related Storage Diseases can be detected early, treated effectively, and go on to live long, healthy and productive lives; a future where doctors and other clinicians are knowledgeable of and able to detect these genetic defects efficiently and with accuracy. In our vision the public at-large will have a general knowledge and understanding of these diseases, and will actively strive to prevent their occurrence. Ultimately, we envision a world where there will no longer be a need for our organization or others like it to exist.

# ISMRD | Board of Directors

**Mark Stark** - President
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Vice President/Fundraising
United States

**John Forman**
Vice President/Research
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**Jackie James**
United States

**Susan Kester**
United States

**Melissa Rust**
United States

# ISMRD | Advisory Board

ISMRD's Board of Directors is assisted in the execution of its mission and goals by the following distinguished members of the international scientific and medical community.

**Steven Walkley,** D.V.M., Ph.D.
Albert Einstein College of Medicine, USA

**Barbara Burton,** M.D.
Children's Memorial Hospital, Chicago, USA

**Sara Cathey,** M.D.
Greenwood Genetic Centre South Carolina, USA

**Alessandra d'Azzo,** Ph.D.
St Jude Children's Research Hospital, USA

**Dag Malm,** M.D., Ph.D.
University Hospital Tromsoe, Norway

**Marc Patterson,** M.D.
Child Neurology
Mayo Clinic, Rochester, USA

**Mark Haskins,** V.M.D., Ph.D.
University of Pennsylvania Veteinary Hospital, USA

**Richard Steet,** Ph.D.
University of Georgia Athens Georgia, USA

**John Hopwood,** Ph.D.
Women & Children's Hospital, Adelaide, Australia

**Thomas Braulke,** Ph.D.
University of Hamburg
Hamburg, Germany

**Charles Vite,** Ph.D.
School of Veterinary Medicine
Philadelphia, USA

# ISMRD | General Information

## Speaker Presentations

After you have registered for the Conference on Friday evening please meet with Mark Stark or Jenny Noble so that your presentation can be loaded onto the computers being used for the conference.

## Registration Desk

The Registration desk will be open on Friday evening from 5pm – 6pm and will open again at 7am on Saturday 28th July.

## Mobile Phones and movement between meetings

Participants are asked to ensure that all mobile phones are switched off during conference sessions. To minimise disturbances in the session rooms whilst presenters are speaking we ask that you remain seated during presentations.

## General questions

ISMRD board members are available at all times to answer your queries.

# ISMRD | Conference Functions

## Welcome Reception

**Friday 27th July 6.30pm – 9.30pm**
A good opportunity to meet colleagues, renew old friendships and make new ones before the conference commences on Saturday.

## Banquet Dinner:

**Saturday 28th July 7.00pm**

We look forward to hosting you all at our Banquet Dinner commencing at 7pm.

## Memorial Service and Balloon Release in Memory of our Special Children

**Saturday 5.10pm**

All delegates are invited to gather at the front entrance of the hotel at 5.10pm for a short memorial service and balloon release in memory of those who have passed away from glycoprotein storage diseases.

Where I have gone, I am not so small.
My soul is as wide, as the world is tall.
I have gone to answer the call, the call
Of the One who takes care of us all.

Wherever you look, you will find me there -
In the heart of a rose, in the heart of a prayer.
On butterflies' wings, on wings of my own,
To you, I'm gone, but I'm never alone -
I'm over the moon, I am home.

Jim Howard

# ISMRD | Children's Program

## Saturday 28th July 2012

**Parents are requested to have their children at the assembly point at 8.00 am.**

Children not going out on the activities program please check with the registration desk for the room location. This is where your caregivers will be waiting for you.

### Off site activities program

| | |
|---|---|
| **7.45 am** | Meet your caregivers |
| **8.30 am** | Board Buses for Aquarium |
| **10.30 am** | Morning Break |
| **12.30pm** | Lunch |
| **1.30pm** | Board bus for Children's Museum |
| **4.30pm** | Return to Hotel |

## Sunday 29th July 2012

**8.15 am** Childcare program held in Bay 2.

Come and enjoy a morning of:
Arts and craft
Card games
Movies
Magician
Face painting
Video Games
Window shopping for those who wish to see whats on offer.

## Children's Activities and Care Arrangements

The childcare room will be open at 7.30am on Saturday for the children who will not be going out on the children's and affected adults' program. It is important that your children are settled in plenty of time for you to move to the beginning of the conference.

## Important notices for parents:

1. It is important that you register your child for care each day.
2. Please meet with the carers and personally hand your children and adults over to them, outlining any particular requirements they may have.
3. We ask that you collect them promptly from the same point at the end of the day.
4. Lunches, drinks and snacks will be supplied for the children and adults. If your loved ones have special dietary requirements please provide their food and make sure it is given to the carers.
5. Please ensure that those going out on the activities program are wearing their name tags, the tee shirts and hats that were handed to you when you registered. Please also ensure that all their personal needs for the day e.g nappies, spare clothes, special food etc are given to the carers.

**Parents: Please ensure that you are seated promptly before the commencement of the conference.**

## Caregivers

We have some truly amazing carers all lined up for your children and adults affected by one of the 9 glycoprotein storage diseases. We want to thank them all for very generously giving up their time to care for our loved ones.

Greenwood Genetic Center

ISMRD

# International Conference for Glycoprotein Storage Diseases 2012

## Scientific Program Saturday 28th July 2012

| | |
|---|---|
| 7.30am - 8.15am | Continental breakfast |
| 8.00 am | Children & Youth Program begins |

## Family Program Saturday 28th July 2012

| | |
|---|---|
| 7.30am - 8.15am | Continental breakfast |
| 8.00 am | Children & Youth Program begins |

## Joint Scientific & Family Session

**Chair:** Sara Cathey

| | | |
|---|---|---|
| 8.30am | Welcome, introduction, opening remarks | **Mark Stark & Sara Cathey** |
| 8.45am | Overview of glycoproteinoses, old and new questions - Looking to contemporary research for answers | **Richard Steet** |
| 9.15am | Effective treatments for rare diseases - How do we get there? | **Emil Kakkis** |
| 9.45am | Questions & answers | |

**10.00am - 10.15am Morning Break**

**Chair:** Marc Patterson

| | | |
|---|---|---|
| 10.15am | Animal models of glycoproteinoses found in nature and in laboratories | **Mark Haskins** |
| 10.40am | Hematopoietic cell transplant in glycoproteinoses | **Troy Lund** |
| 11.15am | Skeletal manifestations of glycoproteinoses: Identification and management | **Jon Davids** |

**12.15 - 1.00 Lunch** Note: **Family sessions begin after lunch in Bay 2**

Greenwood Genetic Center

ISMRD

# International Conference for **Glycoprotein Storage Diseases 2012**

| | | |
|---|---|---|
| | **Chair:** Roger Stevenson | |
| 1.00pm | Mannose 6-phosphate dependent lysosomal enzyme trafficking | **Stuart Kornfeld** |
| 1.20pm | Chemical inactivation of carbohydrate recognition of human β-GUS enhances its ability to cross the BBB and correct neuronal storage in murine MPS VII | **Bill Sly** |
| 1.40pm | Translating science to therapy for galactosialidosis | **Alessandra d'Azzo** |
| 2.00pm | The schindler enzyme behaves differently | **Tim Wood** |
| 2.20pm | Brazilian experience of mucolipidosis II and III | **Ida Schwartz** |
| | **2.45 - 3pm Afternoon break** | |
| | **Chair:** Tim Wood | |
| 3.00pm | Excessive activity of cathespin K is associated with the cartilage defects in a zebrafish model for mucolipidosis type II | **Richard Steet** |
| 3.30pm | Bone disease - before, during and after dysostosis multiplex in ML | **Jules Leroy** |
| 4.00pm | Role of NEU1-regulated lysosomal exocytosis in the pathogenesis of common adult diseases | **Shai White-Gilbertson** |
| 5.00pm | Close of day | |

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|---|---|---|
| | **Chair:** Mark Stark | |
| 1.00pm | The pathway to treatment in glycoprotein storage diseases | **Dawn Laney** |
| 1.20pm | Family experience of transplant procedures | **Mark Stark** |
| 1.40pm | Understanding neurological symptoms and signs | **Marc Patterson** |
| 2.00pm | Genotype phenotype correlation in the glycoproteinoses - Mucolipidosis II and III as examples | **Jules Leroy** |
| 2.30pm | Questions & answers | |
| | **2.45 - 3pm Afternoon break** | |
| | **Chair:** John Forman | |
| 3.00pm | Dental care in glycoproteinoses | **Carlos Salinas** |
| 3.20pm | Family experience of managing dental care for their child with ML II | **Nila Coley** |
| 3.40pm | Overview of eye issues in glycoproteinoses | **Ronald Teed** |
| 4.00pm | Exercise and fitness for individuals with disabilities: Promoting healthy and active lifestyles for everyone | **Joseph Ryan** |
| 5.00pm | Close of day | |

**5.10pm** **Memorial service and Balloon Release in memory of our special children. Please meet at the front entrance of the hotel.**

7pm | ISMRD Gala Dinner

## Scientific Program Sunday 29th July 2012

| | | |
|---|---|---|
| 7.30am - 8.15am | Continental breakfast | |
| 8.00 am | Children & Youth Program begins | |
| | **Chair:** Steve Skinner | |
| 8.30am | Control of lysosomal biogenesis and function by lysosome-to-nucleus signaling | **Roberto Zoncu** |
| 8.50am | Proteomics of the lysosome | **Peter Lobel** |
| 9.30am | Application of high resolution urinary oligosaccharide analysis by MALDI-TOF for the diagnosis of lysosomal storage conditions | **Miao He and Muhammad Ali Pervaiz** |
| 9.50am | Enzyme replacement therapy in children and adolescents with alpha-mannosidosis | **Line Borqwardt** |
| | **10.10am - 10.30am Morning Break** | |

## Family Program Sunday 29th July 2012

| | | |
|---|---|---|
| 7.30am - 8.15am | Continental breakfast | |
| 8.00 am | Children & Youth Program begins | |
| | **Chair:** Carolyn Paisley-Dew | |
| 8.30am | Managing ataxia and seizures | **Marc Patterson** |
| 8.50am | Feeding and nutrition issues in individuals with genetic disorders | **Melinda Whetsell** |
| 9.10am | Partners for life: Palliative care in the lives of children with chronic conditions | **David Steinhorn** |
| 9.30am | Post-secondary education programs for individuals with disabilites | **Joseph Ryan** |
| 9.55am | Questions & Answers | |
| | **10.10am - 10.30am Morning Break** | |

**Chair:** Laura Pollard

| | | |
|---|---|---|
| 10.30am | Enzyme infusion in preclinical canine fucosidosis | **Rosanne Taylor** |
| | Pathophysiology of canine fucosidosis in early disease. | **Jessica Fletcher** |
| 11.10am | Nonsense suppression therapy | **David Bedwell** |

**Chair:** Mark Stark

| | | |
|---|---|---|
| 10.30am | Teen transitions: Tips for the journey | **Dawn Laney** |
| 10.50am | Psychological testing - Why do it? What does it mean? | **Lucia Horowitz** |
| 11.10am | Questions and answers | |
| 11.30am | Summing up of family program | **Mark Stark** |

## Scientific & Family Session Merge

**Chair:** Sara Cathey

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|---|---|---|
| 12.10pm | **Scientific and Family meeting merge -** Final discussion and questions & answers | |
| 12.30pm | Future plans for research | **John Forman** |
| 12.45pm | Summary of Scientific program and closing remarks | **Sara Cathey** |

**1.00 Shared Scientific & Family Lunch**

# Abstracts | Scientific Program

## Overview of glycoproteinoses, old and new questions – Looking to contemporary research for answers | Richard Steet

*Complex Carbohydrate Research Center, The University of Georgia, Athens, Georgia*

The Glycoproteinoses are a group of rare lysosomal storage disorders characterized by the impaired degradation of protein-bound sugar chains within the lysosome. Affected individuals bear mutations in genes that encode for the hydrolytic enzymes themselves or for enzymes that aid in the targeting of these hydrolases to the lysosome. As our understanding of lysosomal biology continues to increase, our view of these diseases has also evolved – with particular regard to how the underlying enzymatic defects eventually lead to the clinical manifestations. In this lecture, an overview of the biochemistry of the Glycoproteinoses will be presented, followed by a summary of recent research advancements. New and emerging themes in the pathophysiology of these disorders, how these new avenues may open up opportunities for treatment and the many ways in which researchers are working together for answers will also be discussed.

# Animal models of glycoproteinoses found in nature and in laboratories | Mark Haskins

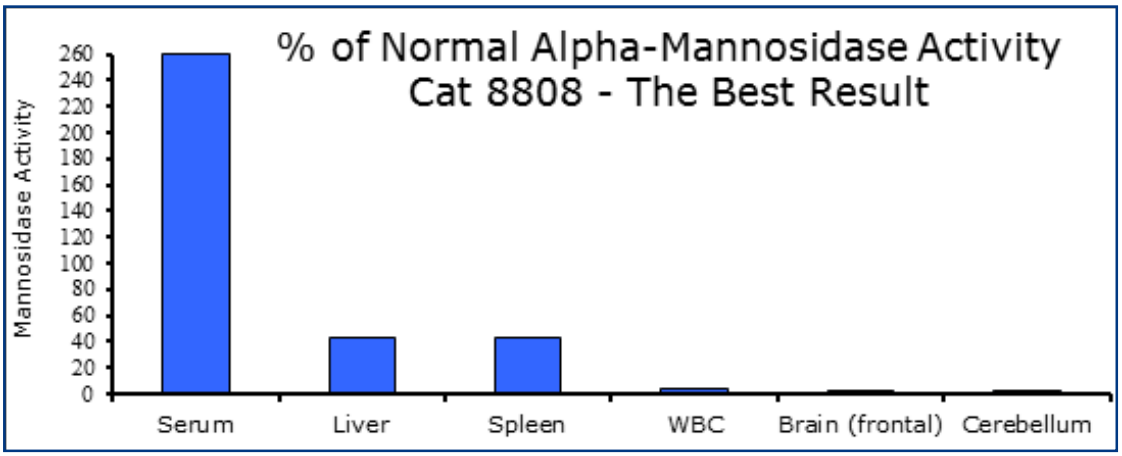
*The University of Pennsylvania, Philadelphia, Pennsylvania*

The chart indicates the animal models for the glycoproteinoses that have been used to understand pathogenesis and evaluate therapies.

| | |
|---|---|
| Aspartylglycosaminuria | KO Mouse |
| Mucolipidosis II | Cat; KO Mouse |
| Mucolipidosis IV | KO Mouse |
| Sialidosis/Galactosialidosis | Mouse; KO mouse |
| a-Fucosidosis | Dog |
| a-Mannosidosis | Cattle; Cat; Guinea Pig; KO Mouse |
| β-Mannosidosis | Goat; Cattle; KO Mouse |

Currently at the University of Pennsylvania, we have colonies of cats with alpha-mannosidosis and mucolipidosis II, dogs with alpha-fucosidosis, and Guinea pigs with alpha-mannosidosis.

There have been reports of several small animal models of lysosomal storage diseases, including Guinea pigs with a-mannosidosis, which were given high doses of recombinant enzyme intravenously that reduced stored substrate in the central nervous system (CNS). No clinical data were presented for the study. We have now treated 11 cats with a-mannosidosis with intravenous, neonatal, retroviral vector-based gene therapy to determine if constant, high levels of mannosidase could affect the CNS clinical signs. While we were able to produce serum activity greater than 2-fold normal, unfortunately no improvement in the development of clinical signs was seen. The chart indicates the % of normal mannosidase activity at 20 weeks of age. Cat 8808 had the highest serum activity.




Currently, we have a 12th cat that is three weeks old and has 4-fold normal serum mannosidase activity, which continues to increase. We hope this will be a kitten that will have a successful clinical outcome.

# Hematopoietic cell transplant for glycoproteinoses

Troy C. Lund

*University of Minnesota, Minneapolis, Minnesota*

The glycoproteinoses are comprised of a group of rare diseases characterized by defects in the cellular processing of carbohydrate-linked proteins. Examples are the mannosidoses (alpha- and beta-), fucosidosis, galactosialidosis, the mucolipidoses (ML II and III), and sialidosis. The defect is in the lysosomal degradation of glycoproteins causing buildup of unprocessed substrates resulting in the various associated "lysosomal storage disease syndromes." There are very few pharmacologic treatments available for this group of diseases. The use of cellular therapy via hematopoietic stem cell transplant (HSCT) with either bone marrow or umbilical cord blood as cell sources has been used as a therapeutic treatment. The rational being that normal lysosomal proteins can travel through the plasma and be taken up by cells for use in lysosomes to degrade substrates. The supply of normal lysosomal proteins by donor hematopoietic cells (following transplant) allows many cells and tissues to return to normal function and may reverse some of cellular dysregulation associated with the lysosomal defect. This phenomenon is referred to as enzymatic or cellular "cross correction." Prototypically, mucopolysaccharidosis I, a lysosomal storage disease concerned with the breakdown of glycosaminoglycans, is an example in which hematopoietic cell transplant is used to cross-correct a lysosomal defect and achieve a neuronal-sparing result (and life-saving).

Similarly, HSCT has been performed in the setting of glycoprotein lysosomal storage diseases with mixed results depending on the disease. I will discuss what is known about HSCT in glycoprotein storage diseases. The knowledge base ranges from case reports in fucosidosis to nearly a dozen transplants for alpha-mannosidosis and even more for ML II (n=23). The outcomes vary as well from: no change in disease and clinical status to possible disease stabilization such as in the use of HSCT in alpha-mannosidosis; there may even be some improvement in some disease manifestations: i.e. cognitive function, gait, and hearing. On the contrary, HSCT for ML-II (I-cell disease) disease has not been published extensively, but 23 patients around the world have received HSCT for ML-II (current study data). It is not clear if HSCT for ML-II alters disease course. Currently, we are performing the first comprehensive study of HSCT outcomes for I-cell disease. Whether HSCT for any glycoprotein disorder can be augmented by gene therapy techniques, recombinant enzyme, or the use of more primordial stem cells (embryonic) is not known, but may hold promise in the future.

## Skeletal manifestations of glycoproteinoses: Identification and management | Jon Davids

*Shriners Hospitals for Sick Children, Sacramento, California*

Musculoskeletal manifestations of the glycoproteinoses are common and signficantly impact function and quality of life. Families are challenged to find orthoapedists familiar with these problems, and experienced in their management. Optimal recognition and management of the most common musculoskeletal manifestations requires an understanding of the disease process, natural history, and treatment options. The goal of this lecture is to educate families about the most common musculoskeletal problems their children face, in order to facilitate decision making for management. The lecture will review the mechanisms of normal skeletal growth and development, disruption of growth in glycoproteinoses, the common elements of dysostosis multiplex, and the rationale for general/ specific management strategies. Time for questions and answers will be included.

## Mannose 6-phosphate dependent lysosomal enzyme trafficking Stuart Kornfeld

*Washington University, School of Medicine, St. Louis, Missouri*

In many cell types of higher eukaryotes mannose 6-phosphate residues on newly synthesized acid hydrolases serve as recognition molecules for binding to Man-6-P receptors in the trans-Golgi network, a key step in their transport to lysosomes. The first step in the synthesis of the Man-6-P signal is mediated by UDP-GlcNAc:lysosomal enzyme N-acetylglucosamine-1-phosphotransferase (Ptase). Ptase is an a2β2γ2 hexamer encoded by two genes: GNPTAB encodes the a,β subunits and GNPTG encodes the γ subunit. Using a multifaceted approach, including analysis of acid hydrolase phosphorylation in mice and fibroblasts lacking the a,β or γ- subunits along with kinetic studies of recombinant a2β2γ2 and a2β2 forms of Ptase, we have explored the functions of the a/β and γ subunits. Our findings indicate that the a/β subunits recognize acid hydrolases as specific substrates and mediate the catalytic function of the transferase whereas the γ subunit enhances the activity of the a/β subunits toward a subset of the acid hydrolases. The γ subunit contains a Man-6-P receptor homology domain that we postulate binds and presents the high mannose glycans of the acceptor acid hydrolases to the a/β catalytic site in a favorable manner. Mice with disruption of the Gnptab gene develop a phenotype similar to, but less severe than, that of patients with mucolipidosis II (mutation in GNPTAB) whereas mice lacking the Gnptg gene have a milder phenotype, as occurs in patients with mutations in the GNPTG gene (mucolipidosis III C). These mutant mice are providing insight into the pathophysiology of MLII and MLIII.

# Chemical inactivation of carbohydrate recognition of human β-GUS enhances its ability to cross the BBB and correct neuronal storage in murine MPS VII | William S. Sly

*St. Louis University School of Medicine, St. Louis, Missouri*

Enzyme replacement therapy has been used successfully in many lysosomal storage diseases. However, correction of brain storage has been limited by the inability of infused enzyme to cross the blood-brain barrier (BBB). We recently reported that PerT-GUS, a form of β-glucuronidase chemically modified to eliminate its uptake and clearance by carbohydrate-dependent receptors, crossed the BBB and cleared neuronal storage in murine mucopolysaccharidosis type VII (MPS VII). In this respect, the chemically modified enzyme was superior to native β-glucuronidase (GUS). Chemically modified enzyme was also delivered more effectively to heart, kidney, and muscle. However, liver and spleen, which express high levels of carbohydrate receptors, received nearly 4-fold lower levels of PerT-GUS compared to native GUS. To confirm and extend these observations, we compared the efficacy of 12 weekly i.v. infusions of PerT-GUS versus native GUS in: (1) delivery of enzyme to brain; (2) improvement of histopathology; and (3) correction of secondary elevations of other lysosomal enzymes. Such correction is a recognized biomarker for correction of neuronal storage. PerT-GUS was superior to native GUS in all three categories. These results provide additional evidence that long-circulating enzyme, chemically modified to escape carbohydrate-mediated clearance, may offer advantages in treating some lysosomal storage diseases that affect brain.

## Translating science to therapy for galactosialidosis | Alessandra d'Azzo

*St. Jude Children's Research Hospital, Memphis, Tennessee*

Galactosialidosis (GS) is a lysosomal storage disease linked to deficiency of the protective protein/cathepsin A (PPCA). Similarly to GS patients, Ppca-null mice develop a systemic disease of the reticulo-endothelial system, affecting most visceral organs and the nervous system. Symptoms include severe nephropathy, visceromegaly, infertility, progressive ataxia, and shortened lifespan. We have recently conducted a preclinical, dose-finding study on a large cohort of GS mice injected intravenously at 1 month of age with increasing doses of a GMP-grade rAAV2/8 vector, expressing PPCA under the control of a liver specific promoter. Treated mice, monitored for 16 weeks post treatment, had normal physical appearance and behavior without discernable side effects. Despite the restricted expression of the transgene in the liver, immunohistochemical and biochemical analyses of other systemic organs, serum and urine showed a dose-dependent, widespread correction of the disease phenotype, suggestive of a protein-mediated mechanism of cross-correction. A notable finding was that rAAV-treated GS mice showed high expression of PPCA in the reproductive organs, which resulted in reversal of their infertility. These results support the use of this rAAV-PPCA vector as a viable and safe method of gene delivery for the treatment of systemic disease in non-neuropathic GS patients and set the stage for a clinical trial targeting children with the late infantile form of GS. In addition, recent research performed in the sialidosis mouse model has suggested that PPCA may have clinical application to a broader range of disease than simply galactosialidosis, by virtue of its ability to enhance the activity of Neuraminidase 1 (NEU1) that PPCA chaperones. NEU1 is not amendable to an enzyme replacement strategy, making a PPCA enhancement approach very attractive for pathologies that include NEU1 downregulation. These findings may therefore position the rAAV-PPCA vector as a potential intervention even for common adult diseases.

## The schindler enzyme behaves differently | Tim Wood

*Greenwood Genetic Center, Greenwood, South Carolina*

Schindler disease (MIM 609241) and Kanzaki disease (MIM 609242) are lysosomal storage disorders which result from a deficiency of alpha-N-acetylgalactosaminidase (NAGA; EC 3.2.1.49). The enzyme deficiency appears to be very rare with less than 20 patients described. NAGA deficient patients can present with and without neurological involvement and with various somatic features including a normal clinical presentation at an early age (<10 years). In an effort to better understand the incidence of this disease, we measured plasma NAGA activity in 210 patients with intellectual disability (ID). NAGA activity was within normal range for all patients suggesting, as expected, it is not a common cause of ID. As part of our broader work in Mucolipidosis II and III, NAGA was measured in fibroblast cultures and plasma from affected patients. While numerous M6P targeted enzymes showed the typical pattern of plasma elevations with low intracellular levels, we were intrigued that ML II and III patient fibroblasts showed high residual NAGA activity on average (about 35%), and 5 patients, regardless of genotype or phenotype, showed intracellular NAGA enzyme activity in the normal range. When we compared plasma from I cell patients (N=35) to controls (N=17), NAGA activity was grossly elevated (mean 2068.1± 96.5 versus 79.5±6; 26X; P<0.001). Immunostaining experiments showed NAGA co-localization with the lysosomal membrane protein LAMP-2, which localizes to lysosomes independently from the M6P pathway. Our data suggest that an intact functionally active alpha-N-acetylgalactosaminidase has been targeted to the lysosome in M6P deficient cells. Taken together, the data provides evidence that NAGA may use a mannose 6 dependent and independent mechanism for targeting to the lysosome.

# Brazilian experience of mucolipidosis II and III

Ida V. D. Schwartz

*Federal University of Rio Grande do Sul, Brazil*

Data from the Brazil MPS Network (www.ufrgs.br/redempsbrasil) indicate that there has been an increase in the number of mucolipidoses II/III (ML II/III) cases diagnosed in recent years in Brazil, probably because more information is available to support clinical suspicion of MPS disorders. Also, there is easier access to MPS diagnostic tests, which in turn is the result of new treatments for some MPS types and from the consequent investment in research in this field. This relative increase in ML II/III diagnoses is hindered by the absence of a simplified, inexpensive biochemical protocol for diagnosis: most laboratories specializing in lysosomal storage disorders require measurement of many plasma/serum and fibroblast lysosomal enzymes, while there is no consensus concerning which enzymes should be investigated; also, DNA analysis is impaired by the polymorphic nature of the genes involved (GNPTAB and GNPTG); and performance of the assay to determine phosphotransferase activity is not simple. In general, data from MPS Brazil Network suggest that patients and families with ML II/III do not have access to the most up-to-date prevention and treatment strategies, due to lack of both knowledge on the part of health professionals and adequate health care interventions. In this lecture, we will address some of the strategies we are developing in Brazil to change this panorama.

# Excessive activity of cathepsin K is associated with the cartilage defects in a zebrafish model for mucolipidosis type II | Richard Steet

*Complex Carbohydrate Research Center, The University of Georgia, Athens, Georgia*

The severe pediatric disorder, mucolipidosis II (ML-II; I-cell disease), is caused by defects in mannose 6-phosphate (Man-6-P) biosynthesis. Patients with ML-II exhibit bone and cartilage defects but the molecular mechanisms that underlie these clinical manifestations are poorly understood. Taking advantage of a zebrafish model for ML-II, we previously showed that the cartilage morphogenesis defects in this model are associated with altered chondrocyte differentiation and excessive deposition of type II collagen, indicating that aspects of development that rely on proper extracellular matrix homeostasis are sensitive to decreases in Man-6-P biosynthesis. To further investigate the molecular bases for the cartilage phenotypes, we analyzed the transcript abundance of several genes in chondrocyte-enriched cell populations isolated from wild-type WT and ML-II zebrafish embryos. Increased levels of cathepsin and matrix metalloproteinase (MMP) transcripts were noted in multiple ML-II cell populations. This increase in transcript abundance corresponded with elevated and sustained activity of several cathepsins (K, L and S) and MMP-13 during early development. Unlike MMP-13, in which higher levels of enzyme was also detected, sustained activity of cathepsin K appeared to result from abnormal processing and activation of this enzyme. Remarkably, inhibition of cathepsin K activity by pharmacological or genetic means not only reduced the activity of this enzyme but also led to a broad reduction in additional protease activity, significant correction of the cartilage morphogenesis phenotype and reduced type II collagen staining in ML-II embryos. Our findings suggest a central role for excessive cathepsin K activity in the developmental aspects of ML-II cartilage pathogenesis and highlight the utility of the zebrafish system to address the biochemical underpinnings of metabolic disease.

# Bone disease before, during and after dysostosis multiplex in ML

Jules Leroy

*Greenwood Genetic Center, Greenwood, South Carolina*

Although the radiographic concept of dysostosis multiplex (DM) applies to several disorders of glycosaminoglycans or glycoprotein storage disorders, the findings and hypotheses presented pertain mainly to the mucolipidoses (ML) due to deficiency of the UDP-GlcNAc-1-phosphotransferase enzyme complex (GNPT). The disorders of intracellular glycoprotein targeting have besides deficient growth and multisystemic consequences of connective tissue disease, a specific set of skeletal abnormalities, termed DM, evident from birth and severe in ML II, apparent from early childhood and variably milder in ML III α/β. The primary enzyme has some residual activity in the latter, but fails completely in the former disorder, a difference with significant clinical implications. Growth retardation in ML II is noticeable in the 3rd trimester of pregnancy and often the neonate is small-for-dates. Early radiographs manifest features of DM and may show in addition transient skeletal abnormalities including periarticular punctuate calcifications (sometimes a prenatal finding in ML II) and more consistently calcified double outline (cloaking) along the diaphyseal surfaces of large tubular bones. In several instances an equally transient hyperparathyroidism has been documented in infancy, but the physiopathological meaning of this concomitant phenomenon remains unclear. The tubular hand and finger bones short and broad at birth, start a postnatal period of intense diaphyseal widening that ceases in early childhood when longitudinal growth comes to a complete halt. Hyperactive intramembranous ossification in bones with failing endochondral metaphyseal growth may explain this phenomenon that is absent or only a mild component of the DM expressed in ML III hands. Patients with ML II do not experience the progressively debilitating large joint disease that accelerates with puberty onset in ML III because of the limited lifespan and lack of weight bearing ambulation that are characteristic of ML II.

Birth weight is consistently within normal limits in ML III α/β patients, where transient skeletal abnormalities are improbable although the later clinical onset precludes radiographic documents. In ML III α/β statural growth is slower than normal and ceases before or in early adolescence. These patients, irrespective of the milder DM, suffer significantly from the morbid long-term consequences of defective GNPT, in both the hard and soft connective tissues. The proximal hip epiphyses are the worst affected of all with painful walking from late childhood and the need for wheelchair support as consequences. Osteopenia, initially non-apparent, becomes severe and painful even at rest and is often accompanied by osteolytic lesions. This inexorably progressive phenomenon occasionally called "bone disease" after DM, is consistently accompanied by equally progressive hardening of all soft connective tissues not only about and in the joints, but in heart valves and bronchopulmonary structures as well. DM and the accompanying late appearing components are shared by patients with other, mainly dysmorphic lysosomal storage disorders. This well known fact supports the hypothesis that the pathogenesis of the common hard and soft connective tissue disease, most morbid late in the clinical courses, is related to continuing leakage of glycoproteins and/or macromolecules into the matrix of connective tissues. This disturbs normal equilibria between signal transduction pathways and/or spuriously activates receptors or alters structural components. Studies in appropriate mammalian animal models should most effectively sort these hypotheses.

## Role of NEU1-regulated lysosomal exocytosis in the pathogenesis of common adult diseases | Shai White-Gilbertson

*Eda Machado, Diantha van de Vlekkert, Simon Moshiach, Erik Bonten, Alessandra d'Azzo.*
*St Jude Children's Research Hospital, Memphis, Tennessee*

Of the four mammalian sialidases, Neuraminidase 1 (NEU1) is the most abundant. NEU1 resides in the lysosome where it cleaves a2,6- or a2,3-linked terminal sialic acids from the saccharide chains of glycoconjugates. Genetic deficiency of NEU1 results in the glycoprotein storage disease sialidosis. Our lab developed a mouse model of this disease, which has yielded novel insights into the molecular mechanisms driving the pathology seen in sialidosis patients, with unexpected and important implications for other disease conditions. We discovered that NEU1 negatively regulates a process called lysosomal exocytosis. In the absence of NEU1, its natural substrate Lysosomal Associated Membrane Protein (LAMP1) accumulates and facilitates the trafficking of lysosomes to the plasma membrane (PM). These lysosomes are then poised to dock at the PM, fuse, and release lysosomal luminal content extracellularly. As a result of this exocytic phenotype, resident lysosomal proteins, including active proteases such as cathepsins, are aberrantly ejected from the cell, degrading the extracellular matrix (ECM). Changes in the ECM leave tissues more vulnerable to invasion by non-native cells and, indeed, we observed aberrant infiltration of fibroblasts into affected muscle beds of sialidosis mice. This phenotype was reminiscent of the cellular invasion seen in many cancers, which are known to extensively modify their ECM. We have therefore investigated the possible relevance of NEU1 and lysosomal exocytosis to cancer cell behavior.

## Control of lysosomal biogenesis and function by lysosome-to-nucleus signaling | Roberto Zonco

*Whitehead Institute for Biomedical Research , Cambridge, Massachusetts*

Long viewed as the cells' 'garbage bin', the lysosome is emerging as a key metabolic compartment that undergoes dynamic changes in size and composition in response to the metabolic needs of the cell. Our understanding of how lysosomal biogenesis is regulated according to cellular demand is still in its infancy. Transcription Factor EB (TFEB) was recently identified as a master regulator of lysosomal gene expression. As part of a transcriptional program that enhances the catabolic potential of the cell, TFEB drives the production of new lysosomes and boosts the function of existing ones. However, the factors that regulate TFEB are currently unknown.

I will present evidence that the master growth regulator, mechanistic Target of Rapamycin Complex 1 kinase, controls TFEB activity. mTORC1 is a sensor of lysosomal status; in response to nutrients, mTORC1 phosphorylates TFEB on the lysosomal surface, preventing it from reaching the nucleus. Starvation or loss of lysosomal function inactivates mTORC1, allowing TFEB to move to the nucleus and upregulate lysosomal gene expression. Thus, mTORC1 and TFEB are part of a lysosome-to-nucleus signaling mechanism that links sensing of lysosomal status by mTORC1 to regulation of lysosomal biogenesis by TFEB.

A hallmark of many lysosomal storage diseses (LSDs) is the loss of basic functions, such as the lysosome's ability to fuse with other membrane compartments and to traffic metabolically important substrates, which are controlled transcriptionally by TFEB. Thus, manipulations of the mTORC1-TFEB pathway may represent a promising approach to boost lysosomal function and correct metabolic derangement in LSDs.

## Proteomics of the lysosome | Peter Lobel

*Rutgers University, Piscataway, New Jersey*

Lysosomes are membrane delimited organelles with an acid internal pH that are essential components of the digestive tract of eukaryotic cells, representing the terminal destination for autophagic and endocytic pathways. The primary function of the lysosome is to degrade biological macromolecules and to transport catabolic end products to other cellular locations. Defects in this pathway result in human disease, the most clearly defined being the over forty different lysosomal storage disorders that arise from mutations in genes encoding lysosomal proteins.

To date, over sixty different soluble hydrolytic enzymes (proteases, glycosidases, lipases, nucleases, phosphatases, sulfatases, etc) and accessory proteins have been identified that work in concert in the lysosome to degrade complex biological macromolecules to simple constituents. In addition, there are ~60 lysosomal membrane proteins that are involved in export of catabolites, maintaining the ionic environment of the lysosome, and other processes. However, our understanding of lysosome biology and disease is incomplete, with new lysosomal proteins and disease genes continuing to be identified. I will describe proteomic approaches directed at advancing our knowledge in these areas.

# Application of high resolution urinary oligosaccharide analysis by MALDI-TOF for the diagnosis of lysosomal storage conditions

Miao He & Muhammad Ali Pervaiz

*Xia B(1,) Asif G (1), Pervaiz MA(1), Botha EG(1), Wood T(2), He M1.,(1) Emory University, Atlanta, Georgia; (2) Greenwood Genetics Center, Greenwood, South Carolina*

The glycosylation is an important modification step for many biological compounds. The degradation of glycoprotein and glycolipid is predominantly lysosomal. Lysosome contains a serial of glycosidase and other enzymes required for the complete degradation of glycoprotein or glycolipid. When the lysosomal enzyme was deficient, free oligosaccharides, glycoamino acids, glycopeptides and glycolipids accumulate in urine. Elevations in specific urinary oligosaccharides or glycoamino acids were often indicative of specific lysosomal disorders, such as alpha-mannosidosis, fucosidosis, sialidosis, galactosialidosis, Mucolipidosis II or III, Pompe, GM1, Gaucher, Aspartylglucosaminuria and GM2 etc. The traditional one-dimensional thin-layer chromatography method for urine oliogsaccharides analysis has limited resolution and sensitivity, therefore provides no structural information and that is often needed for diagnoses. We have developed a high resolution urinary oligosaccharides and glycoamino acids profiling by Matrix-assisted laser desorption/ionization-Time of flight/Time of flight (MALDI-TOF/TOF). 100-500 µl urine (0.09mg creatinine) was loaded on a Seppak C18 column. The free oligosaccharides and glycoamino acids were purified by activated carbon carbograph solid phase extraction column. Both free oligosacchrides and glycoamino acids were then subject to permethylation, and analyzed by MALDI-TOF/TOF using positive reflector mode. Using pattern recognition, for the first time, we successfully identified two cases of Nieman Pick A disease by urinary oligosaccharide screening. Nieman Pick A disease is a condition that led to metabolites from multiple glycolipids accumulating in the urine. Our studies demonstrated that the urinary oligosacchrides and glycoamino acid analysis by MALDI-TOF/TOF provides a robust clinical test to screen for oligosaccharidosis and other related storage disorders.

# Enzyme replacement therapy in children and adolescents with alpha-mannosidosis | Line Borgwardt

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## Background

Alpha-mannosidosis (AM) is a rare LSD caused by alpha-mannosidase deficiency including intellectual disabilities, facial characteristics and hearing impairment.
A recombinant human alpha-mannosidase enzyme (rhLAMAN) has been developed for weekly intravenous enzyme replacement therapy (ERT). We present the preliminary data after 12 months of treatment.

## Material and Methods

This is a phase I-II study to evaluate safety and efficacy of the rhLAMAN.
10 patients (7-17 y) were treated. The efficacy evaluation of the motor function (6MWT, 3MSCT, BOT-2), cognitive function (Leiter-R), measurement of oligosaccharides in serum, urine and CSF and CSF-Tau-protein and GFA-protein were investigated.

## Results

Oligosaccharides: S-, U- and CSF-oligosaccharides decreased, respectively by 88.6 % (CI -92.0 -85.2, p<0.001), 54.1 % (CI -69.5- -38.7, p<0,001), 25.7% (CI –44.3- -7.1, p<0.05).
Biomarkers: CSF-Tau-protein and GFA-p decreased respectively 15 % , p<0.009) and 23.1% (CI -54.4 – 8.2, NS).
Motor function: Improvements in 3MSCT (31 steps (CI 6.8-40.5, p<0.01) and in 6MWT (60.4 meters (CI –8.9 -51.1, NS) were achieved.
Cognitive function: Improvement in the total Equivalence Age of 4 months (0.34) was achieved in the Leiter R test (CI -0.2-0.8, NS).

## Conclusion

These data suggests that rhLAMAN is an encouraging new treatment for patients with AM. The study will continue for a total of 1½ years where final conclusions can be drawn.

# Enzyme infusion in preclinical canine fucosidosis | Rosanne Taylor

*]1]Taylor Rosanne M., (1)Kondagari Gauthami S., (1)Fletcher Jessica L., (1)Williamson Peter, (2)Hemsley Kim M., and (2) Hopwood John J. (1)Faculty of Veterinary Science, The University of Sydney, NSW, Australia (2)Lysosomal Diseases Research Unit, Adelaide Hospital for Women and Children, North Adelaide*

AIM
Canine fucosidosis is an authentic model for progressive, neurovisceral lysosomal storage caused by α-L-fucosidase deficiency in children. The impact of repeated intracisternal enzyme infusions on the clinical, biochemical, molecular and pathological features of early fucosidosis were investigated. The canine neural pathology commences before 2 months of age with early vacuolation and perivascular storage, which is accompanied by pyramidal neuronal loss, astrocytosis, myelin loss, microgliosis and axonal spheroid formation throughout the central nervous system by 4 months age, well in advance of the onset of clinical signs of motor dysfunction. Biochemical, pathological and molecular markers were evaluated to determine the effects of intermittent direct enzyme replacement.

METHODS
2 month old English Springer spaniels were grouped as; affected enzyme treated (AET), affected vehicle treated (AVT) and control vehicle treated (CVT) with 3 per group. The enzyme or vehicle was administered by intracisternal infusions monthly for 3 treatments and we measured CSF biomarkers for inflammation. At necropsy neural tissue was analysed for enzyme activity (EA), substrates, gene expression and neuroinflammatory markers were quantified in immunostained sections using image analysis.

RESULTS
Enzyme activity was found throughout the brain, spinal cord and many viscera of AET, with wide variation, some regions with up to 10% of control EA, compared to enzyme-deficient AVT tissues. EA was detected in cerebrospinal fluid at 48 hours but not at 4 weeks after infusion. Substrate accumulation was reduced in many neural tissues of AET compared to AVT. Astrocytosis and microgliosis were observed early in disease correlating with proinflammatory cytokine expression. Inflammatory markers were reduced after treatment, but not normalized, despite this very early intervention. Biomarkers in CSF Interleukin 6 and 10 increased with progressive fucosidosis while monocyte chemoattractant protein 1 and keratinocyte chemoattractant both decreased in response to treatment.

CONCLUSIONS
Enzyme replacement therapy by monthly intracisternal infusion had a distinct, positive effect on fucosidosis, producing widespread, low levels of EA, with reduced substrate storage and improved molecular and pathological markers of inflammation in tissue and CSF. These subtle changes (compared with our bone marrow transplantation studies in fucosidosis) likely reflect the transient, low levels of EA achieved in the brain, following rapid removal of infused enzyme from cerebrospinal fluid.

# Pathophysiology of canine fucosidosis in early disease

## Jessica Fletcher

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Fucosidosis, caused by a deficiency of a-L-fucosidase due to mutations in the FUCA1 gene is a severe neurovisceral lysosomal storage disease that afflicts children and English Springer spaniel dogs. Canine fucosidosis is the only available animal model of this disease and recent characterisation of the cellular pathology has revealed that lysosomal vacuolation of neurons and glia, neuronal apoptosis, axonal dystrophy, neuroinflammation and myelin loss occur as early as 2 months of age, well before the onset of clinical signs at approximately 6 to 8 months. Despite detailed characterisation of the cellular pathology, the molecular pathways that trigger these cellular changes remain unclear. Studies to elucidate fucosidosis pathophysiology were performed on neural tissue from preclinical fucosidosis-affected dogs and age-matched unaffected controls. These included gene expression profiling of the frontal cortex, characterisation of oligodendrocyte and myelin abnormalities in the central nervous system (CNS) and examination of cytokine expression in cerebrospinal fluid (CSF). Where possible studies were extended to samples from animals with early and advanced clinical signs. Findings revealed that cytokine (CCR1, CCR5) and cathepsin (CTSC, CTSD, CTSS) genes contributing to neuroinflammation and apoptotic processes were upregulated in preclinical fucosidosis frontal cortex and that myelin genes (CNP, MAG, MAL, OPALIN) were downregulated. Follow up examination of oligodendrocytes in the CNS demonstrated a significant ($P < 0.001$) reduction of oligodendrocyte populations, consistent with hypomyelination. Elevated CSF levels of the chemokines MCP-1/CCL2 and KC/CXCL1 were identified at 8 weeks of age and these levels increased over a period of 2 months. Together these findings help demystify some of the molecular pathways that underlie fucosidosis neuropathology and may contribute to identifying novel therapeutic targets and developing informative markers of disease progression and treatment response in the future.

## Nonsense suppression therapy | David Bedwell

*University of Alabama at Birmingham, Birmingham, Alabama*

Nonsense suppression therapy is a novel strategy for treating protein deficiencies attributable to in-frame premature termination codons (PTCs). Nonsense suppression drugs increase the aminoacyl-tRNA accommodation frequency at a PTC located in the ribosomal A site, resulting in amino acid incorporation into the nascent polypeptide at the position of the PTC. This "readthrough" mechanism circumvents translation termination at PTCs by resuming translation elongation in the correct reading frame to generate a full-length protein. Many studies have shown that this approach can restore partial protein function in models of a number of genetic diseases. However, a recent cystic fibrosis (CF) clinical trial suggested that current suppression therapy agents provide only a limited therapeutic response in CF patients, suggesting that new strategies to enhance PTC suppression are needed. Suppression therapy may be relatively ineffective in many individuals due to nonsense-mediated mRNA decay (NMD), a conserved eukaryotic cellular pathway that targets PTC-containing mRNAs for degradation. NMD reduces the effectiveness of suppression therapy by depleting the PTC-containing mRNA pool available for translation and subsequent PTC suppression. I will present the results of a recent study testing the hypothesis that attenuating NMD to elevate PTC-containing mRNA levels may restore higher levels of functional protein for MPS I-H via PTC suppression, and thus provide a greater therapeutic benefit in patients with a range of genetic diseases.

# Abstracts | Family Program

## The pathway to treatment in glycoprotein storage diseases

Dawn Laney

*Emory University, Decatur, Georgia*

Although there are no Food and Drug Administration approved targeted treatments for Glycoprotein Storage Diseases (GSDs), this presentation combines the vision of the ISMRD's crystal ball with current research in a neighboring lysosomal diseases to discuss possible future treatments in GSDs. Discussion will take us through current preclinical research that could benefit GSDs and suggest steps that will bring us closer to effective targeted treatments.

# Understanding neurological symptoms and signs

Marc C. Patterson

*Mayo Clinic, Rochester, Minnesota*

Many children and adults with glycoprotein storage diseases have neurologic symptoms and signs. Neurologists use these findings to make diagnoses in two steps: first, to localize the affected site or sites in the brain, spinal cord or peripheral nerves and second, to use features of the history to generate a specific diagnosis or a list of potential diagnoses (differential diagnosis).

Understanding basic neuroanatomy is helpful in understanding the causation and evolution of neurologic dysfunction in children. In general, weakness, that is the inability to generate power in the limb, trunk or head and neck muscles, results from injury to structures of the so-called motor unit, which comprises the nuclei of the cranial nerves and their peripheral nerve components or the motor unit (anterior horn cells in the spinal cord, the peripheral nerves, the junction between the nerve and the muscle (neuromuscular junction), and the muscle itself). Injuries to the pathways that communicate between the cerebral cortex, the basal ganglia (deep nuclei in the brain), the cerebellum and the anterior horn cells or cranial nerve nuclei generally cause only transient weakness, but tend to impair the nature of movement and can also alter muscle tone. Muscle tone is a confusing concept. Many people equate this with power, but this is not the case. Disorders that affect the motor unit cause a reduction in muscle tone (hypotonia) that is typically accompanied by weakness. Injuries to the pathways above the motor unit may cause increased or decreased tone in association with impaired initiation, quality and accuracy of movement.

Disorders involving the spinal cord may produce paralysis, weakness, spasticity, and impaired sensation at and below the level of the injury to the spinal cord, plus disturbed bladder and bowel function. Disorders of the brainstem (which includes the medulla, pons and midbrain), cause difficulties with chewing, swallowing, articulation of speech, movement of the eyes, sensation of the head and neck and sometimes with smell, taste, coordination and balance. Disorders of the basal ganglia (deep gray nuclei in the brain) cause a variety of movement disorders which may include decreased movement as seen in Parkinson's disease and related conditions, or increased movement as is seen with tics or chorea. Disorders that affect the cerebral cortex affect memory and the ability to think and reason, and may cause complex disorders of vision, hearing and sensation as well as giving rise to epileptic seizures.

## Genotype phenotype correlation in the glycoproteinoses - Mucolipidosis II and III as examples | Jules Leroy

*Greenwood Genetic Center, Greenwood, South Carolina*

Knowledge of basics in biology and genetics is a prerequisite to understanding the essential aspects of the glycoproteinoses, the group of inborn errors of metabolism that interest us most specifically in this address. Remarkably the reverse is true as well. Molecular biologists and doctors of medicine have increased knowledge of relevant aspects of biology by caring for and studying hereditary metabolic disorders. Because genetics has a major causal role in these disorders, some introductory notes on general and molecular genetics will precede the main topic: the mucolipidoses caused by mutations in the GNPTAB gene that encodes the enzyme UDP-GlcNAc-1-phosphotransferase. The delineation of I-Cell disease in 1966, later called Mucolipidosis II (ML II) has initiated this clinical and scientific subject. The disorders' clinical onset is at or even before birth. It severely affects connective tissues, soft as well as hard, and is associated with moderate intellectual disability. The course is progressive with fatal outcome often before mid-childhood. Each patient has inherited a so-called severe mutation in the gene mentioned above, from her or his normal parents.
Mucolipidosis III, called pseudo-Hurler polydystrophy , when first described, turned out to share the pathogenesis with ML II. Its onset is in early childhood. It has initially a milder phenotype and progresses considerably slower. The cognitive ability of ML III patients is within normal limits. The patients have inherited at least one mild GNPTAB mutation from one of the healthy parents. One cannot ignore the more morbid features of ML III that become apparent from adolescence. The symptomatic treatment with cyclic IV-infusion of bisphosphonates often alleviates bone and joint pain, notoriously immobilizing features in the older ML III patient. Causal treatment remains unavailable for either ML II or ML III. Some information on the rare but interesting patients that are clinically intermediate between ML II and ML III will also be provided.

## Dental care in glycoproteinoses | Carlos Salinas

*Medical University of South Carolina, Charleston, South Carolina*

Abstract not recieved prior to printing.

## Family experience of managing dental care for their child with ML II

Nila Coley

*Cedartown, Georgia*

This presentation is a discussion of oral hygiene issues and how they can affect children with Mucolipidosis Type II. The importance of early intervention in gingival health is addressed. Locating the right provider and knowing what questions to ask is key to positive outcomes. Simple oral hygiene practices specifically for children with storage diseases will also be discussed, including their prophylactic effect on the overall health of children with storage diseases. Finally, medical procedures that are used to treat gum overgrowth will be presented for discussion.

## Overview of eye issues in glycoproteinoses | Ronald Teed

*Children's Eye Specialists, South Carolina*

The glycoprotein lysosomal storage diseases present with a spectrum of ophthalmic manifestations. The current literature on this class of disease remains sparse. Nonetheless, both classic and atypical ocular findings are expected in diseases such as the mannosidoses, fucosidosis, galactosidosis, the mucolipidoses, the sialidoses, and Schindler disease. This lecture will survey the common eye findings in these disorders, highlight those findings that may have diagnostic or prognostic value, and discuss the real-world implications that these findings have for afflicted patients.

## Exercise and fitness for individuals with disabilities: Promoting healthy and active lifestyles for everyone | Joseph Ryan

*Clemson University, Clemson, South Carolina*

Children with disabilities are at increased risk of health risk factors including obesity often due to low levels of physical activity and limited participation in sports. However, organized adaptive sports programs are increasingly available for individuals with disabilities. This presentation provides recommendations for families on how to involve their children with disabilities in schools and other community-based recreational facilities enabling them to live healthier and happier lives. Dr. Ryan will share lessons learned from seven years experience as the founder and Director of several therapeutic recreation leagues for athletes with disabilities including soccer, baseball and equine therapy.

## Managing ataxia and seizures | Marc C. Patterson

*Mayo Clinic, Rochester, Minnesota*

Ataxia refers to incoordination of movement. Ataxia generally results from malfunction of the cerebellum or its connections, although sensory disorders and frontal lobe lesions can occasionally cause similar findings. We generally take smooth movement for granted, but it relies on extremely complex circuitry. As any muscle is moving, a continuous stream of information is being fed back to the brain regarding the tension of the muscles themselves, the relative position of different parts of limbs and joints, and the speed of movement. This information is processed through a number of structures, particularly the cerebellum which then provides feedback to the muscles to make minute and continuous adjustment to the rate and intensity of their contraction. Thus, if the pathways sending information to the cerebellum, the circuitry of the cerebellum itself or the information flow from the cerebellum to the muscles is impaired, there will be a loss of smooth, coordinated movement leading to the so-called decomposition of movement (dysdiadochokinesis) that is characteristic of cerebellar disease. This is often accompanied by tremor. In some cases, jerky movements referred to as myoclonus may also accompany ataxia. Unfortunately, it is much easier to cause ataxia than to improve it. The cerebellum is very sensitive to drugs, including medicines to treat epilepsy and anxiety and, of course, most adults are aware of the effects of alcohol which has a profound effect on the function of the cerebellum.
The mainstay of treatment for ataxia is physical, occupational and speech therapy. Some physical aids can be of help; providing patients with weights to attach the limbs can increase resistance to movement and thus reduce irregular movements, albeit at the cost of considerably increased energy expenditure.

Epileptic seizures are the manifestation of sudden excessive discharge of the gray matter of the brain, particularly the cerebral cortex. The manifestations depend on the site from which these excessive discharges arise. The management of epileptic seizures is rationally approached by identifying the cause of seizures if possible and if this is susceptible to specific treatment, offering such interventions. In most cases, however, such treatment is not possible and a more generalized approach using antiepileptic drugs is required. These drugs come in a number of classes which affect the flow of charged molecules across the membranes of neurons. Because such drugs cannot be targeted to the specific population of neurons generating the epileptic seizures, a variety of adverse effects commonly occur.

Epilepsy (recurrent unprovoked seizures) occurs in 1 to 2 percent of the population and is thus a common family of disorders. About 70 percent of cases can be readily controlled with one or two medications. Of the remainder, some will respond to multiple medications, but other avenues of therapy include dietary management with the ketogenic diet or, in some cases, the modified Atkins diet, the use of vagus nerve stimulation or surgery. We will discuss these options in more detail during the presentation.

## Feeding and nutrition issues in individuals with genetic disorders

Melinda Whetsell

*Greenwood Genetic Center, N. Charleston, South Carolina*

Individuals with special health care needs often experience feeding problems. Feeding issues, such as the inability or refusal to eat certain foods, may be due to neuromotor problems, obstructive lesions or psychosocial problems. The nutritional consequences of feeding problems include abnormal weight gain (too much or too little), poor growth in length/height, vitamin and mineral deficiencies and developmental delay. The goals of this presentation are to review common feeding challenges and discuss interventions to improve the nutritional status of individuals with special health care needs.

## Partners for life: Palliative care in the lives of children with chronic conditions | David Steinhorn

*Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois*

Traditionally, palliative care has been thought of as the prelude to hospice and end-of-life care. For many adult and some pediatric patients that continues to be the model that best meets the needs of the patients and their families. However, pediatric palliative care has forged new frontiers for palliative care by recognizing that early referral and extended care by an integrated palliative care team can enhance the quality of life of children and their families when definitive cure is not yet possible. This presentation will explore some of the ways in which pediatric palliative care can fill some of the gaps. In addition, the issue of caregiver burden will be addressed and explored in the context of caring for children living with incurable disease.

## Post-secondary education programs for individuals with disabilities

Joseph Ryan

*Clemson University, Clemson, South Carolina*

This presentation will describe the core components and necessity of postsecondary transition programs for students with disabilities. Dr. Ryan founded ClemsonLIFE (Learning is for Everyone) a post secondary education program at Clemson University under the belief that all young adults must develop skills and understanding about themselves and the world around them in order to fully participate in society and become successful, contributing adults. The ClemsonLIFE program specializes in preparing young adults with disabilities for employment and living independently.

## Teen transitions: Tips for the journey | Dawn Laney

*Genetic Counselor/Research Coordinator, Emory University, Decatur, Georgia*

Transition is defined as the passage from one place or stage of life to another. One important transition is the movement of a teen with a glycoprotein storage condition entering adulthood to manage their own healthcare at the appropriate level. Effective transition involves the involved teen, their parents, other family members, healthcare professionals, and related community agencies. The objective of this talk is to discuss this transition period and provide helpful resources and suggestions for individuals facing this exciting life milestone.

## Psychological testing - Why do it? What does it mean?
## Lucia Horowitz

*Greenwood Genetic Center, Greenwood, South Carolina*

Psychological testing is used throughout life and impacts a variety of decisions from diagnostic assessment to educational placement to job interests and placement to the best type of living arrangement, etc. This is especially true for individuals with disabilities. Results from these assessments can often be difficult to understand and may seem different from what parents feel their child is really like.

The goal of this presentation is to help parents and caregivers better understand these tests and how such testing can be useful when making important life decisions.

# ISMRD | Speaker Profiles

## Line Borgwardt, M.D.

Line Borgwardt is a physician and PhD student at the Department of Clinical Genetics at the University hospital of Copenhagen, Rigshospitalet, Denmark. She received her MD at Copenhagen University in 2003.

In the field of metabolic diseases, her interests are focused in particular on lysosomal storage diseases, in which she is doing her PhD about alpha-Mannosidosis.

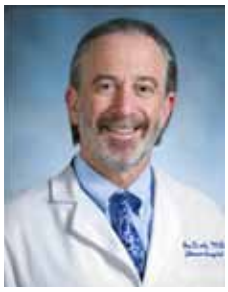
Line Borgwardt has a background in paediatric and is in specialist training in Clinical Genetics.
for the treatment of non-neuropathic galactosialidosis that will be in a clinical trial in the near future.

## David Bedwell, Ph.D.

The goal of research in the Bedwell lab is to understand the mechanistic details of translation termination and whether pharmacological agents can be used to suppress nonsense mutations that cause human diseases. Dr. Bedwell is a Professor of Microbiology, Genetics, and Cell Biology at the University of Alabama at Birmingham School of Medicine. He is also a member of the Editorial Board of the Journal of Biological Chemistry, a Fellow of the American Academy of Microbiology, and standing member and chair of the NIH Molecular Genetics B study section.

## Nila Coley

My name is Nila Coley. My husband, Jon, and I are the proud parents of two beautiful girls, Jonalin (9) and Harper (5). Jonalin has Mucolipidosis Type II. Until recently I have been a stay at home mom. Now that both children are in school, I am pursuing a career in public service. Having obtained a Bachelor of Science degree in Political Science I work for the Probate Court as well as consulting on several local political campaigns. In 2005, after Jonalin was diagnosed, we met Dr. Jules Leroy and Dr. Sara Cathey and became the pioneer family for isolating mutations in DNA for Mucolipidosis. Since that time, we have continually researched medical technologies and procedures that may benefit Jonalin, always giving careful consideration to potential associated risks. We believe that our efforts have been fruitful and are so grateful that Jonalin continues to thrive. Our family resides in Cedartown, Georgia USA.



## Jon R. Davids, M.D.

Jon R. Davids MD is a board certified Pediatric Orthopaedic Surgeon who is the Ben Ali Chair and Professor of Orthopaedics at the University of California Davis School of Medicine; and the Assistant Chief of Orthopaedic Surgery and Medical Director of the Motion Analysis Laboratory at the Shriners Hospitals for Children in Sacramento, California. Jon has worked for the Shriners Hospital system since 1993. He is also on the medical staff at the Shriners Hospital in Greenville, South Carolina, where he served as Chief Surgeon from 2006 through 2011.

Jon received his undergraduate degree in Latin American Studies from Brown University, attended Harvard Medical School, completed a residency in Orthopaedic Surgery at the University of Colorado, and a fellowship in Pediatric Orthopaedics at the University of California San Diego Children's Hospital and Health Center. Jon has published over 70 articles in peer review journals, and serves on the editorial boards of the Journal of Pediatric Orthopaedics and Gait and Posture. He has written 26 textbook chapters on a variety of topics in pediatric orthopaedics. Jon has lectured extensively at regional, national and international levels, teaching gait analysis interpretation and clinical applications for children with cerebral palsy, myelodysplasia, and limb deficiency.

## Alessandra d'Azzo, Ph.D.

Alessandra d'Azzo graduated with a degree in Biology at the University of Milano, Italy, and completed her doctorate in Genetics in 1973. She did her postdoctoral training in the Department of Cell Biology and Genetics at the Erasmus University in Rotterdam, The Netherlands, and later completed a thesis for a second doctorate degree at the same University that was awarded cum laude. From 1982 to 1984, Dr. d'Azzo was a Fogarty International Fellow in the Genetics and Biochemistry Branch of the NIH, where she strengthened her experience and interest in lysosomal degradation and lysosomal diseases. She was appointed Assistant and then Associate Professor at the Erasmus University Rotterdam, where she developed her scientific program, and taught first and second year medical students. Dr. d'Azzo joined the Faculty at St. Jude Children's Research Hospital in Memphis USA in 1993 and is currently a Full Member of the Genetics Department; she holds an Endowed Chair in Genetics and Gene therapy at St. Jude; and is an Adjunct Professor in the Department of Anatomy and Neurobiology at the University of Tennessee Health Sciences Center. Dr. d'Azzo is a member of the scientific advisory board for the National MPS Society; she is a member of the Society for Inherited Metabolic Disorders, the American Society of Human Genetics, the American Society of Neurochemistry, the American Society of Gene Therapy, and the International Society for Oligosaccharidosis and Related Disorders. Her work on lysosomal storage diseases has led to numerous key publications in journals such as Cell, Genes and Development, Molecular Cell, Developmental Cell and Nature.

The primary scope of her research is to understand mechanisms involved in the pathogenesis of lysosomal storage disorders, particularly those affecting glycoprotein and glycosphigolipid metabolism, and to translate this information to the development of appropriate therapies for children affected by these diseases. Her lab has generated faithful mouse models for several lysosomal storage diseases, which have allowed for in depth studies on the impact of enzyme deficiency and accumulation of specific metabolites on cell and tissue homeostasis. She successfully used these laboratory animals to implement preclinical therapeutic modalities, including enzyme replacement, bone marrow transplantation, and in vivo and ex vivo gene therapy. Her accomplishments include the discovery of the primary defect in the lysosomal storage disease, galactosialidosis, the discovery of a new muscle-specific ubiquitin ligase involved in myogenesis and muscle homeostasis and the development of a gene therapy approach for the treatment of non-neuropathic galactosialidosis that will be in a clinical trial in the near future.

## Jessica Fletcher

Jessica Fletcher is a PhD student at the Faculty of Veterinary Science, The University of Sydney. In 2008, she completed a Bachelor of Animal and Veterinary Bioscience (Hons I) during which she developed an in interest in genomics and comparative neuropathology. Her PhD research uses canine animal models and genomic tools to investigate the molecular pathology that occurs in inherited brain disease, particularly in the lysosomal storage disorders, Krabbe disease and fucosidosis. She hopes that by understanding how molecular disease pathways give rise to pathology and clinical signs, more effective tools to treat and manage these disorders will be developed.

## Mark Haskins, V.M.D., Ph.D.

Dr. Haskins has established the Mucopolysaccharidosis (MPS) I, IIIB, VI, MPS VII, Mucolipidosis II, Glycogen storage disease IV, alpha-mannosidosis, Neimann-Pick C, fucosidosis, and Krabbe dog and cat models of human lysosomal storage diseases. He has 30 years of experience in the management of the colonies, investigating pathogenesis, performing gene therapy and drug treatments, clinical evaluations including radiology, and post mortem tissue collection.

**Positions and Employment**

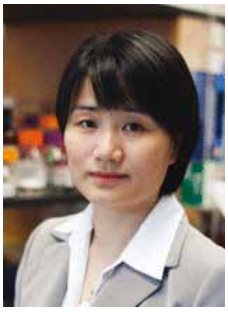
1975-1978 - NIH-GM Trainee in Medical Genetics, School of Medicine, University of Pennsylvania, Phila, PA
1978-1981 - Research Assistant Professor of Pathology, University of Pennsylvania, Philadelphia, PA
1981-1984 - Assistant Professor, Pathology and Medical Genetics, University of Pennsylvania, Phila., PA
1984-1991 - Associate Professor, Pathology and Medical Genetics, University of Pennsylvania, Phila.,
1991 - Professor, Pathology and Medical Genetics, School of Veterinary Medicine, University of Pennsylvania
2006 - Head, Laboratory of Pathology and Toxicology, School of Veterinary Medicine, University of Pennsylvania

**Other Experience and Professional Memberships**

American Society of Gene and Cell Therapy
American Veterinary Medical Association
International Society for Mannosidosis and Related Diseases
National Mucopolysaccharidosis Society
Gene Therapy and Inborn Errors Study Section, NIH, 2004, 2007, 2008

**Grant Reviews**

- INSERM (Institut national de la sante de la recherché medicale) site visit, Paris, France, 2006
- Medical Research Council, London, England, 2006
- French National Research Agency and the French Institute for Research on Rare Diseases, 2006
- Ad Hock Review, Neurological Sciences and Disorders-B, June 2007, February 2008
- Scientific Evaluation Committee, French National Research Agency, 2008-present
- Advisory Committee, National Center for Canine Models of Duchenne Muscular Dystrophy, 2008-present
- Grant Review – European Transnational Consortia for Rare Disease Research, 2009
- Ad Hock Review, Molecular and Cellular Endocrinology Study Section, February 2010



## Miao He, Ph.D.

Miao He's major research interests include new genetic disorders in protein glycosylation, mitochondrial fatty acid beta oxidation, amino acid catabolism and cholesterol biosynthesis. The primary focus of my research is to biochemically characterize these new disorders and to study the associations between metabolism and immune regulations in human. The primary focus of my clinical work is to transform traditional biochemical tests to automated and multiplexed tests with higher sensitivity and specificity for the diagnosis of a variety of metabolic genetic disorders.

## Lucia T Horowitz, Ph.D.

Lucia T. Horowitz, Ph.D. is a licensed and certified School Psychologist who has been a member of the Clinical Research Faculty at Greenwood Genetic Center since 2008. Prior to coming to GGC, Dr. Horowitz's specialties included autism assessment and treatment, assessment and treatment of individuals with learning disabilities, ADHD, and communication disorders, and treatment of children and adolescents with behavioral and emotional problems. Since coming to GGC, Dr. Horowitz has developed skills in the assessment of children with metabolic disorders, Angelman syndrome, and individuals affected by various glycoproteinoses. Dr. Horowitz has been a team member for two of Dr. Cathey's glycoproteinoses natural history clinics- one at GGC and the others in Australia and New Zealand.

Dr. Horowitz received a B.S. in Biology from Furman University and an M.A. and Ph.D. from the University of South Carolina. She has worked as a School Psychologist, Director of Child and Adolescent Services for a regional Mental Health Center, State Director of Training for the Autistic Program of the SC Department of Mental Health, and Director of the CARE Center with autism diagnostic clinics in Charleston, Columbia, and the Medical University of South Carolina as part of the Autism Division of the South Carolina Department of Disabilities and Special Needs. She was in private practice for 13 years doing assessments and therapy with children and adolescents and their parents. She has also done training and consultation for school districts, treatment centers for emotionally disturbed children, developmental pediatric programs, and groups of teachers and therapists in Russia.

## Emil D. Kakkis, M.D., Ph.D.

Dr. Kakkis is best known for his work over the last 18 years to develop novel treatments for rare disorders. He began his work developing an enzyme replacement therapy (Aldurazyme®) for the rare disorder MPS I, with minimal funding and support. The struggle to get the therapy translated from a successful canine model to patients succeeded due to the critical financial support of the Ryan Foundation, a patient organization formed by Mark and Jeanne Dant for their son Ryan.

Aldurazyme development was later supported by BioMarin Pharmaceutical and eventually their partner Genzyme leading to FDA approval in 2003. During his tenure at BioMarin, Dr. Kakkis guided the development and approval of two more treatments for rare disorders, MPS VI and PKU, and has contributed to the initiation of 7 other treatment programs for rare disorders, three of which are now in clinical development.

After 11 years at BioMarin, Dr. Kakkis left industry to initiate an effort to improve the regulatory and clinical development process for rare diseases. In early 2009, Dr. Kakkis launched and funded the Kakkis EveryLife Foundation to accelerate biotech innovation for rare diseases. The Foundation initiated a campaign to improve the regulatory and clinical development process for rare diseases. In just over a year, 160 patient organizations and physician society partners have endorsed the Campaign.

Dr. Kakkis has founded Ultragenyx™ to return to development of drugs for rare diseases. For many rare diseases, reasonable science exists that needs to get translated to patients. He will build on his previous experiences and will assemble an experienced team to efficiently develop treatments for rare diseases.
Dr. Kakkis is board certified in both Pediatrics and Medical Genetics. He graduated from Pomona College, magna cum laude and received combined M.D. and Ph.D. degrees from the UCLA Medical Scientist Program and received the Bogen prize for his research. He completed a Pediatrics residency and Medical Genetics Training Fellowship at Harbor- UCLA Medical Center. He became an assistant professor of Pediatrics at Harbor-UCLA Medical Center from 1993 to 1998 where he initiated the enzyme therapy program for MPS I. In 1998, he joined BioMarin where he remained for 11 years in various titles eventually as Chief Medical Officer, before leaving in 2009.

## Stuart Kornfeld, M.D.

The major focus of our research is protein trafficking and organelle biogenesis. Specifically, we study the phosphomannosyl targeting system which functions in the delivery of newly synthesized acid hydrolases to lysosomes. Defects in this intracellular protein transport pathway give rise to severe lysosomal storage diseases. A key step in this pathway is the selective phosphorylation of mannose residues on the high mannose glycans of the acid hydrolases by UDP-GlcNAc: lysosomal enzyme N-acetylglucosamine-1-phosphotransferase (Ptase). This transferase is an α2β2γ2 hexameric protein. Currently we are studying the role of these subunits in the recognition of the common protein determinant of acid hydrolases and in the binding of the high mannose units of these acceptors. These studies utilize recombinant Ptase with and without its γ subunit or with mutations in specific domains. We also are studying mice with disruptions of the genes encoding the α/β or γ subunits to follow the tissue specific development of pathologic changes. In a second project, we are investigating the role of adaptor protein-1 (AP-1) and the GGA (for Golgi-localized, γ-ear containing, ARF-binding) proteins in the packaging and transport of the Man-6-P receptors with bound acid hydrolases at the trans-Golgi network. These studies utilize mice with disruptions of the genes encoding the GGAs. This work is supported by an NIH grant with Merit Status.

## Dawn Jacob Laney, MS, CCRC

After earning a Bachelor of Arts in Biology and History at Trinity College in Hartford, Connecticut, Dawn Jacob Laney received a Master of Science in Human Genetics from Sarah Lawrence College in Bronxville, New York. Currently, Ms. Laney is an Instructor and a Program Leader at the Emory Lysosomal Storage Disease Center in the Department of Human Genetics, Emory University, in Atlanta, Georgia. Her position involves seeing lysosomal storage disorder patients in clinic, coordinating enzyme-replacement therapy infusion treatments, developing a genetic infusion center and co-coordinating a Gaucher disease clinical research trial. She is also the author of two children's books "Joe Learns About Fabry Disease" and "My Brother, MPS, and Me!". Ms. Laney is a member of the Emory Institutional Review Board (a research oversight committee charged with ensuring that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in approved research studies). She is a member of the National Society of Genetic Counselors and the American College of Medical Genetics.

## Jules Leroy, M.D., Ph.D.

Jules Leroy is currently Emeritus Professor and Chairman of the Departments of Paediatrics and Medical Genetics, Ghent University Hospital and Medical School, Ghent, Belgium. Remains professionally active as a senior visiting scholar at the Greenwood Genetic Center, Greenwood, South Carolina, USA. As a 1959 graduate from the Ghent University Medical School, he holds a MS in Biochemistry (1961) from his Alma Mater. He trained in Paediatrics at Children's Hospital Medical Center, Boston, Mass., and in Genetics and Paediatrics at the University of Wisconsin, Madison, Wisconsin, where he obtained a PhD degree in Genetics (1967). His doctoral thesis under Dr. R.I. DeMars holds the initial clinical and pathogenetic delineation of I-Cell disease, Mucolipidosis II, topic that remains at the top of his scientific interest and still kindles his wider interest in lysosomal pathology, the glycoproteinoses, the field of storage disorders and in the process of intracellular trafficking of macromolecules.

## Peter Lobel, Ph.D.

Peter Lobel is a Member of the Center for Advanced Biotechnology and Medicine (CABM) and a Professor of Pharmacology at Robert Wood Johnson Medical School (RWJMS) in Piscataway, New Jersey, USA. He also serves as the Director of the RWJMS-Rutgers University Biological Mass Spectrometry Facility. He received his Ph.D. in Biochemistry in 1986 from Columbia University in New York. He initiated his long standing research into mannose 6-phosphate receptors and the lysosomal enzyme targeting pathway during postdoctoral studies with Stuart Kornfeld at Washington University School of Medicine in St. Louis. Lobel's laboratory has developed proteomic approaches to characterize components of the lysosome and to investigate the role of lysosomal proteins in human disease. This research enabled discovery of the basis for two fatal hereditary childhood neurodegenerative diseases, late infantile neuronal ceroid lipofuscinosis and Niemann Pick type C2 disease.

## Troy Lund, M.D., Ph.D.

Dr. Lund is an assistant professor at the University of Minnesota in the Division of Pediatric Blood and Marrow Transplant, and a member of the Metabolic Disease Program. His clinical and laboratory research focuses on several aspects of hematopoietic stem cell transplant (HSCT) for metabolic disease including: overcoming graft failure, predicting transplant outcomes in metabolic disease, and understanding the fundamental cellular dysregulation of several metabolic storage diseases. Specifically, his lab is looking at the cytokines profiles searching for new biomarkers in the plasma and cerebral spinal fluid of patients with metabolic storage disease as they relate to inflammatory pathways as well as the pathways of oxidative stress. Through the identification of these pathways he hopes to bring to the clinic new therapies or adjuvant therapies to help children receiving HSCT for a storage disease to achieve better outcomes and more thoroughly attenuate disease manifestations including cardiac and skeletal problems. Secondly, he focuses on the use of stem cells to model storage disease in the in vitro setting with the goal of developing high throughput assays to search for new compounds to ameliorate storage disease pathology.

## Marc C. Patterson, M.D.

Marc Patterson was born and educated in Australia. After graduating from the Faculty of Medicine at the University of Queensland with First Class Honors in 1981, he trained in Medicine, Pediatrics and Neurology, and was admitted to fellowship of the Royal Australasian College of Physicians. He traveled to the US in 1988, where he completed further training in pediatrics and child neurology at Mayo Graduate School of Medicine, and a fellowship in neurometabolic diseases with Roscoe Brady at the National Institutes of Health.

After completing his training, Dr. Patterson joined the staff of Mayo Clinic, where he became Consultant, Associate Professor and Director of the Child Neurology Training Program. He moved to New York on 2001 to become Professor and Director of Pediatric Neurology at Columbia University. In July, 2007, Dr Patterson returned to Mayo Clinic, where he is now Professor of Neurology, Pediatrics and Medical Genetics, Chair of the Division of Child and Adolescent Neurology and Director of the Child Neurology Training program. He currently serves as a member of the Neurology topic advisory group for revision of the ICD-10 of the World Health Organization, and leads the Education Core of the NIH-funded Lysosomal Disease Network. He recently completed service as a member of the Committee to Review Adverse Effects of Vaccines of the Institute of Medicine.

He recently completed a term as Chair of the Neurodevelopmental Disabilities Examination Committee of the American Board of Psychiatry and Neurology, and joined the Neurology Part C Examination Committee in 2011. He has served on the Potamkin Prize Subcommittee, the Residency Examination Subcommittee and the Sidney Carter Award Subcommittee of the AAN, and as a councilor and member of the Archives and International Affairs committee of the Child Neurology Society. Dr Patterson is an active member of the ANA, and currently serves on the Annals Oversight Committee. He is a councilor for the Child Neurology Section of the AAN.

Dr. Patterson's research has focused on rare diseases in children, including multiple sclerosis and neurometabolic disorders, with special interests in Niemann-Pick disease, type C, other lysosomal diseases (including glycoproteinoses) and congenital disorders of glycosylation, areas in which he has published and spoken widely; he has more than 225 publications of all types. His research has been supported by NIH, Mayo Clinic, private foundations and industry. He is strongly committed to advocacy for children with rare diseases, and works closely with several patient support groups in the US and overseas.

## Muhammad Ali Pervaiz, M.D.

Dr. M. Ali Pervaiz is the Biochemical Genetics Lab co-director at Emory Genetics Laboratory. He also works as a clinical metabolic geneticist in the Division of Medical genetics, Emory University, where he sees patients with inborn errors of metabolism including lysosomal storage diseases. Dr. Pervaiz obtained his Medical Degree from Hamdard University in Pakistan. He completed an Internal Medicine Residency at New York Medical College. He subsequently trained in Clinical Genetics and Clinical Biochemical Genetics at Emory University and Mayo Clinic, respectively.

## Joseph Ryan, Ph.D.

Dr. Joe Ryan serves as the Associate Director of Research for Clemson University's School of Education, and as Vice President for the International Council for Children with Behavioral Disorders (CCBD). He has taught students with special needs from grades K through 12 across a variety of educational settings, including resource and self-contained classrooms, special day schools, and a residential treatment center. Professional interests include: single subject research, behavior management, psychotropic medications, therapeutic recreation, and post secondary transition services. He teaches courses in applied behavior analysis, behavior management, emotional/behavioral disorders, and single subject research design. He has published 36 journal articles and book chapters, and frequently consults and speaks at national and international professional conferences. He is the founder and Director of ClemsonLIFE (Learning is for Everyone), a post secondary transition program for students with cognitive disabilities. He is also the founder and Director of several Clemson therapeutic recreation programs in baseball, soccer and equine therapy.

## Carlos F Salinas, D.M.D.

Dr. Salinas is a Professor and Director in the Division of Craniofacial Genetics, Department Pediatric Dentistry and Orthodontics, College of Dental Medicine, Medical University of South Carolina (MUSC), Charleston SC. He also serves as Director of the MUSC Craniofacial Anomalies and Cleft Palate Team and as Co- Director of the Clinical Resource Core at the Center for Oral Health Research.

Dr. Salinas is a dentist and graduated from the University of Chile. He was awarded an NIH-Fogarty International Fellowship in Medical Genetics at the Johns Hopkins School of Medicine. In 1974, he joined MUSC, where he has developed most of his academic career. Dr Salinas' areas of research interest include the study of craniofacial anomalies, the ectodermal dysplasias, the relationship between oral dental disease and systemic disorders, and health disparities in special care dentistry. He has edited five books and published over 100 scientific publications. He has organized several national and international symposia in the area of birth defects that involve craniofacial and oro-dental structures.

In regards to Special Care Dentistry, since 1999 Dr Salinas has organized annual continuing education courses on the "Diagnosis and Treatment of Patients with Special Health Care Needs ". Over 2000 dental professionals have participated in these courses.

He has also developed and implemented the South Carolina Dental Directory for Individuals with Special Health Care Needs <http://www.handsonhealth-sc.org/dental>.

The directory lists 400 dentists and facilitates access and referrals of individuals with special health care needs. The directory was distinguished in Best Practices 2007 and has served as a model for similar directories in West Virginia and in Florida. Since 2001, Dr Salinas has organized and implemented the Special Smiles program in conjunction with the SC Special Olympics. Over 1000 athletes have received dental screenings and oral health education. In 2011, he was elected President elect of the ADPD/ Special Care Dentistry association.

Dr Salinas has been awarded grants from NIH- Fogarty, NIH/NIDCR, NIH/NCRR, DHHS-MCHB, SCDDC, SCDHEC, RWJF, Duke Endowment, SCDHHS, and SCDA.

Dr Salinas is member of the Special Care Dentistry Association, American Cleft Palate and Craniofacial Association, American Society of Human Genetics, the Society of Craniofacial Genetics, International Association for Dental Research, Hispanic Dental Association, SC Dental Association/ADA, and the SC Oral Health Coalition. He has been elected Fellow of the American College of Dentists and the Pierre Fauchard Academy and as Distinguished Scholar of the National Academy of Practices, Academy of Dentistry.

Dr. Salinas served for ten years as a volunteer dentist for the less privileged people at the East Cooper Community Outreach Dental Clinic in Mount Pleasant, South Carolina. He also served as member of the Executive Committee and Board member for the same organization.

## Ida Vanessa Doederlein Schwartz, M.D., Ph.D.

Ida Vanessa Doederlein Schwartz earned her M.D. and Ph.D. degrees in Brazil. Both her Masters and Ph.D. were related to lysosomal storage disorders, and Mucolipidosis is now one of her main research lines. She is Associate Professor of the genetics department of the Universidade Federal do Rio Grande do Sul, and coordinator of the Inborn Metabolic Clinics at Medical Genetics Service-Hospital de Clínicas de Porto Alegre, Brazil, an international reference center for diagnosis and treatment of lysosomal storage disorders. Among her awards and recognitions received, some stand out, such as: L'OREAL /Brazilian Academy of Sciences for Women in Science (2007), and affiliation to the Brazilian Academy of Sciences (2008).

## William S. Sly, M.D.

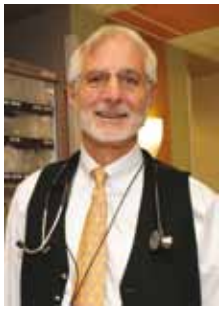
William S. Sly, M.D is an internationally known physician/scientist who, except for sabbatical years at Oxford and Stanford, has spent his entire academic career in St. Louis. Following completion of his M.D. training at Saint Louis University School of Medicine, he trained in Internal Medicine at Washington University and in research laboratories at the NIH, in Paris, and in Madison, Wisconsin before joining the faculty at Washington University, where he directed the Division of Medical Genetics for 20 years. He was appointed the Alice A. Doisy Professor and Chairman of the Edward A. Doisy Department of Biochemistry and Molecular Biology at Saint Louis University in 1984. In February 2007, he was also named the inaugural holder of the James B. and Joan C. Peters Endowed Chair in Biochemistry and Molecular Biology.

Dr. Sly has made important contributions to several research areas. His group described the first patient with MPS VII (Sly syndrome) and worked with collaborators at The Jackson Laboratory to characterize the mouse model of this disease. He headed studies that identified the mannose-6 phosphate and mannose receptors that target enzymes to lysosomes, which provided the rationale for enzyme replacement therapy in Gaucher's disease and other lysosomal storage diseases. Dr. Sly also identified the first inherited deficiency of a human carbonic anhydrase, CA II, and defined the biochemical and molecular genetics of this disorder. His laboratory has since characterized many other carbonic anhydrases and produced mouse models of several CA deficiencies. Dr. Sly has also done research on hereditary hemochromatosis, collaborating on studies leading to the cloning of the HFE gene and identification of the product it encodes, and demonstrating that the HFE gene knockout produces iron storage resembling hemochromatosis in the mouse.

Dr. Sly has received many awards and honors for his research accomplishments, including induction into the National Academy of Sciences in 1989, the Coriell Medal from the Coriell Institute for Medical Research in Camden, New Jersey, for pioneering work in human genetics, the Peter H. Raven Lifetime Achievement Award from the Academy of Science of St. Louis, the Marcel Simon Prize from The Hemochromatosis Society in Albany, NY, the World Congress of Iron Metabolism in Cairns, Australia, the Distinguished Scientist Award from the Clinical Ligand Assay Society, the Passano Foundation Award, and the Burlington Northern Foundation Faculty Achievement Award for outstanding research. Dr. Sly has served on the Scientific Review Board and Medical Advisory Board for the Howard Hughes Medical Institute, the Board of Scientific Overseers for the Jackson Laboratory, the Board of Trustees of Kenrick-Glennon Seminary and on many scientific societies and other foundations. He serves on the editorial boards for several journals and is an editor for the classic metabolic text, The Metabolic and Molecular Bases of Inherited Diseases.

## Richard Steet, Ph.D.

Richard Steet is a native of upstate New York, Dr. Steet received his Ph.D. from the University of Colorado-Boulder in 2000. Following postdoctoral studies in the laboratory of Dr. Stuart Kornfeld at Washington University School of Medicine in St. Louis, he began his independent research career at the Complex Carbohydrate Research Center on the University of Georgia campus in 2006. His laboratory studies the pathophysiology of glycosylation-related disorders, with a primary focus on mucolipidosis II, using zebrafish models and cultured cells. Recent research in his laboratory (in collaboration with his wife and colleague, Dr. Heather Flanagan-Steet) is beginning to yield new insight into the pathogenic mechanisms associated with the cartilage and bone symptoms of ML-II. Dr. Steet has served on the Professional Advisory Board for ISMRD since 2011.



## David Steinhorn, M.D.

Dr. Steinhorn is a graduate of the University of Minnesota Medical School with post-graduate training in Pediatric Hepatology and Critical Care. He was a Bioethics consultant under Arthur Caplan, PhD, at the University of Minnesota Hospitals and Clinics where he was an attending physician in Pediatric Critical Care. Following relocation to the Children's Hospital of Buffalo, Dr. Steinhorn undertook post-doctoral clinical training in Hospice and Palliative Care under Dr. Robert Milch. At that time, Dr. Steinhorn became the first medical director and assisted in creating the Essential Care Program in Buffalo. He is currently a Professor of Pediatrics at Northwestern University Feinberg School of Medicine and serves as Medical Director of the Bridges Palliative Care Program at Children's Memorial Hospital in Chicago. Dr. Steinhorn was the Medical Director for the Children's Memorial Hospital Integrative Medicine Initiative for seven years which undertook research on complementary medicine in children. He has training in energy medicine, Fourth Way traditions, yoga meditation, and shamanism. Dr. Steinhorn continues to serve full-time as an attending physician primarily in cardiac critical care. He is on the medical advisory board of Almost Home Kids, a transitional care facility in suburban Naperville, and is the advisor to the Northern Illinois Pediatric Palliative Care Coalition. He is certified by the American Academy of Pediatrics in Critical Care and Hospice and Palliative Medicine as well as by the American Academy of Hospice and Palliative Care. Dr. Steinhorn serves on the Executive Committee and was a founding member of the AAP's Section on Hospice and Palliative Medicine.

Above all else, Dr. Steinhorn's professional and personal passion is to bring light and awareness of spirit into institutional pediatric healthcare and into his own life.

## Rosanne Taylor, Ph.D.

Rosanne Taylor is Dean of The Faculty of Veterinary Science, The University of Sydney, Australia, a globally accredited school which has just celebrated its first century. Rosanne's research in comparative neuroscience explores the pathogenesis and treatment of inherited brain damage in animal models. Rosanne completed a large animal internship, worked in small animal practice, completed PhD and postdocs in Sydney and University of Pennsylvania, where she demonstrated the value of stem cell, enzyme replacement and gene therapies for treating lysosomal storage diseases (ACVS Clunies Ross research award, 1999). As Manager of the NSW Government Animal Welfare Branch she oversaw implementation of Australia's first comprehensive legislation for animal research. Rosanne teaches veterinary physiology and stem cell biology. As Associate Dean and Chair of Learning and Teaching (2001-7) and ProDean (2008-9) she led curriculum and cultural change in teaching (recognized by Faculty's Pfizer and Grace Mary Mitchell Awards 2001, Vice Chancellors Teaching Award 2002, Vice Chancellor's team award 2009). She is a member of the AAVMC Governance and JVME editorial boards, AVA education committee. While Rosanne's current student projects include gene dysregulation in Krabbe mice, pathogenic mechanisms in canine tumours, and ways to improve veterinary education, her greatest passion lies with understanding and reversing the impact of fucosidosis on the nervous system.

## Ronald Teed, M.D.

Ronald GW Teed, MD is a Board Certified Pediatric Ophthalmologist in solo practice at Children's Eye Specialists, LLC. He is a member of the American Academy of Ophthalmology, American Association of Pediatric Ophthalmology and Strabismus, and the American Academy of Pediatrics. Dr. Teed received a bachelor degree from the University of Arizona, and a medical degree from the University of Michigan. Following an internship at Oakwood Hospital in Dearborn, MI, he completed a residency in Ophthalmology at Vanderbilt University in Nashville, TN. He then completed a fellowship in pediatric ophthalmology and strabismus at the Storm Eye Institute, Medical University of South Carolina, where he stayed on the faculty for four years. His major interests are complicated strabismus, retinopathy of prematurity and ophthalmic genetics and development.

## Melinda Whetsell, MS, RD, LD

Melinda Whetsell is a registered dietitian with the Greenwood Genetic Center metabolic team in Charleston, South Carolina. She received her BS in Food Science from Clemson University in 1989 and her MS in Nutrition Sciences from the University of Alabama at Birmingham in 1991. Melinda joined the Greenwood Genetic Center in 2002 from the South Carolina Department of Health and Environmental Control where she was a nutritionist for the Children's Rehabilitative Services program for 10 years. Melinda has over 20 years experience providing nutrition services to children with special health care needs. She currently provides medical nutrition therapy for individuals with inborn errors of metabolism. Melinda is a member of Genetic Metabolic Dietitians International, the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) and the South Carolina Dietetic Association.

## Dr. Shai White-Gilbertson, Ph.D.

Dr. White-Gilbertson received her Masters in Clinical Research and PhD with a focus on tumor immunology from the Medical University of South Carolina in 2009. Her dissertation work examined the role of three proteins in the progression of cancer. These proteins, cFLIPs, CerS6, and EF2, each contribute to malignant cell growth or resistance to chemotherapeutic drugs through their own distinct mechanisms, elucidated by Dr. White-Gilbertson over a series of six published papers. Dr. White-Gilbertson then joined the lab of Dr. Alessandra d'Azzo, a leader in studying lysosomal storage diseases. Dr. d'Azzo had recently developed a hypothesis about a possible application of the lab's extensive physiological work in sialidosis to the field of cancer. This project has generated many new insights and some of this work will be presented for the first time at this conference.

## Tim Wood, Ph.D.

Dr. Wood came to the Greenwood Genetic Center (GGC) as a clinical laboratory fellow in 2000. After completing fellowships in clinical molecular and clinical biochemical genetics, he was named assistant director of the biochemical genetics laboratory. In 2006 he was promoted to director. Dr. Wood is currently ABMG certified in both clinical molecular and clinical biochemical genetics.

Dr. Wood is a member of the Society of Inherited Metabolic Disease, the Society for the Study of Inborn Errors of Metabolism, the American Society of Human Genetics and is a fellow of the American College of Medical Genetics. Dr. Wood serves on the board of directors for the Southeastern Regional Genetics Group and is a member of the South Carolina Newborn Screening Advisory Committee.
The GGC biochemical laboratory has a broad focus and serves as a clinical testing center for South Carolina, including follow up testing for expanded newborn screening. The laboratory specializes in the diagnosis of lysosomal storage disorders, congenital disorders of glycosylation, and creatine biosynthesis disorders.

## Roberto Zoncu, Ph.D.

Robert Zoncu's participation in the design of the Advanced Microscopy Facility for the Program in Cellular Neuroscience, Neurodegeneration and Repair (CNNR) at Yale University. Responsibilities included the purchase and installation of a Total Internal Reflection Fluorescence (TIRF) and a Spinning Disk Confocal microscopy systems, and coordination with Yale architecture and engineering for design of the imaging center.

Collaboration with the Keck Imaging Center at the Whitehead Institute for the selection and purchase of a combined TIRF/Spinning Disk imaging system (Andor Technology). Personally upgraded the system to enable STORM imaging capability.

June 2010: Selected participant to the 1st Stochastic Optical Reconstruction Microscopy (STORM) Workshop Harvard University Dept of Chemistry, Cambridge MA.

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# ISMRD | Professional Delegates

| | |
|---|---|
| **Stephanie Cagle** | USA |
| **Neena Champaigne, M.D.** | USA |
| **Barb Gordon, M.D.** | USA |
| **Steve Kinsman, M.D.** | USA |
| **Julie Jones, Ph.D.** | USA |
| **Mike Lyons, M.D.** | USA |
| **Laura Pollard, Ph.D.** | USA |
| **Ulrike Reiss, M.D.** | USA |
| **Steve Skinner, M.D.** | USA |
| **Roger Stevenson, M.D.** | USA |
| **Jacquelyn Evans** | USA |
| **Heather Flanagan-Steet, Ph.D.** | USA |

# ISMRD | Family Delegates

| | | | |
|---|---|---|---|
| **Patricia Adkins** | Mucolipidosis type II | Parent | USA |
| **Joan Allen** | Alpha Mannosidosis | Parent | Canada |
| **Steve Allen** | Alpha Mannosidosis | | Canada |
| **Sherriee Amour** | Mucolipidosis type III | Parent | USA |
| **Jane Andrews** | Mucolipidosis type II/III | Parent | USA |
| **William Andrews** | Mucolipidosis type II/III | Parent | USA |
| **Andre Andrews** | Mucolipidosis type II | | USA |
| **Dakota James** | Mucolipidosis type III | Sibling | USA |
| **Savahnna James** | Mucolipidosis type III | | USA |
| **Maria – Elena Cardenas** | Mucolipidosis type II/III | Parent | USA |
| **Sergio Cardenas** | Mucolipidosis type II/III | | USA |
| **Nila Coley** | Mucolipidosis type II | Parent | USA |
| **Jon Coley** | Mucolipidosis type II | Parent | USA |
| **Jonalin Coley** | Mucolipidosis type II | | USA |
| **Lucinda Crompton** | Alpha Mannosidosis | Parent | USA |
| **Brandon Crompton** | Alpha Mannosidosis | Parent | USA |
| **Alyssa Crompton** | Alpha Mannosidosis | | USA |
| **John Forman** | Alpha Mannosidosis | Parent | New Zealand |
| **Patrick Gaffner** | Alpha Mannosidosis | | USA |
| **Kristopher Gaffner** | Alpha Mannosidosis | | USA |
| **Martin Gaffner** | Alpha Mannosidosis | | USA |
| **Ivan Garcia** | Galactosialidosis | | Canada |
| **Andrea Gates** | Mucolipidosis type III | Parent | USA |
| **Kevin Gates** | Mucolipidosis type III | Parent | USA |
| **Spencer Gates** | Mucolipidosis type III | | USA |

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|---|---|---|---|
| **Sydney Gates** | Mucolipidosis type III | Sibling | USA |
| **Sarah Geisert** | Alpha Mannosidosis | Sibling | USA |
| **Debera Hoffman** | Alpha Mannosidosis | Parent | USA |
| **Richard Hoffman** | Alpha Mannosidosis | Parent | USA |
| **Tyler Huneault** | Sialidosis | | Canada |
| **Jackie James** | Mucolipidosis type III | Parent | USA |
| **Anna James** | Mucolipidosis type III | | USA |
| **Susan Kester** | Mucolipidosis type III | Parent | USA |
| **Mary Kimmet** | Mucolipidosis type II | Parent | USA |
| **Kevin Kimmet** | Mucolipidosis type II | Parent | USA |
| **Andrea Kimmet** | Mucolipidosis type II | | USA |
| **Kathleen King** | Alpha Mannosidosis | Parent | USA |
| **Fernando Laca** | Mucolipidosis type III | Parent | USA |
| **Jean Leonard** | Fucosidosis | Parent | United Kingdom |
| **David Leonard** | Fucosidosis | Parent | United Kingdom |
| **Christopher Leonard** | Fucosidosis | | United Kingdom |
| **Michelle McGee** | Mucolipidosis type III | Sibling | USA |
| **Colin McKay** | Alpha Mannosidosis | Parent | Canada |
| **Kathleen McKay** | Alpha Mannosidosis | Parent | Canada |
| **David McKay** | Alpha Mannosidosis | | Canada |
| **Jenny Noble** | Mucolipidosis type III | Parent | New Zealand |
| **Paul Noble** | Mucolipidosis type III | Parent | New Zealand |
| **Carolyn Paisley-Dew** | Fucosidosis | Parent | Australia |
| **Ashley Pauls** | Galactosialidosis | Parent | Canada |
| **Patricia Pauls** | Galactosialidosis | Grandparent | Canada |
| **Birthe Roll** | Mucolipidosis type III | Parent | Norway |
| **Trus Roll** | Mucolipidosis type III | Parent | Norway |
| **Pernille Roll** | Mucolipidosis type III | | Norway |
| **Melissa Rust** | Mucolipidosis type II | Parent | USA |
| **Matthew Rust** | Mucolipidosis type II | Parent | USA |
| **Rebecca Rust** | Mucolipidosis type II | Sibling | USA |
| **Meghan Rust** | Mucolipidosis type II | | USA |
| **Ida Ryan** | Sialidosis | Parent | Canada |
| **Elizabeth Sibert** | Mucolipidosis type III | Parent | USA |
| **Jesse Sibert** | Mucolipidosis type III | Parent | USA |
| **Mary Sibert** | Mucolipidosis type III | | USA |
| **Robert Sibert** | Mucolipidosis type III | Sibling | USA |
| **Jennifer Simpson** | Mucolipidosis type III | Parent | Canada |
| **Matthew Simpson** | Mucolipidosis type III | | Canada |
| **Rhonda Skipper** | Alpha Mannosidosis | Parent | USA |
| **David Skipper** | Alpha Mannosidosis | Parent | USA |
| **Mark Stark** | Alpha Mannosidosis | Parent | USA |
| **Robert Stark** | Alpha Mannosidosis | | USA |
| **Matthew Stark** | Alpha Mannosidosis | Sibling | USA |
| **Julie Taravella** | Aspartylglucosaminuria | Parent | USA |

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|---|---|---|---|
| **Daniel Taravella** | Aspartylglucosaminuria | | USA |
| **Alexander Taravella** | Aspartylglucosaminuria | | USA |
| **Starla Thomas** | Mucolipidosis type III | Parent | USA |
| **Sheldon Thomas** | Mucolipidosis type III | Parent | USA |
| **Skylar Thomas** | Mucolipidosis type III | | USA |
| **Dale Thompson** | Alpha Mannosidosis | | USA |
| **Matthew Thompson** | Alpha Mannosidosis | | USA |
| **Lonnie Tice** | Mucolipidosis type III | | USA |
| **Chris Tice** | Mucolipidosis type III | Sibling | USA |
| **Sarah Tice** | Mucolipidosis type III | Sibling | USA |
| **Pam Tobey** | Mucolipidosis type III | Parent | USA |
| **Autumn Tobey** | Mucolipidosis type III | | USA |
| **Adina Trestianu** | Mucolipidosis type III | | Italy |
| **Bianca Trestianu** | Mucolipidosis type III | | Italy |
| **David Vidal** | Aspartylglucosuminuria | Sibling | Spain |
| **Sylvia Webb** | Mucolipidosis type II/III | Parent | Australia |
| **Charles Webb** | Mucolipidosis type II/III | Parent | Australia |
| **Tegan Webb** | Mucolipidosis type II/III | | Australia |
| **Grace Webb** | Mucolipidosis type II/III | | Australia |
| **Jonathan Whitehurst** | Mucolipidosis type II | Parent | USA |
| **Inha Zahnetova** | Alpha Mannosidosis | Parent | Russia |
| **Daryia Zahnetova** | Alpha Mannosidosis | | Russia |
| **Noor Zaidi** | Alpha Mannosidosis | Parent | USA |
| **Sadia Zaidi** | Alpha Mannosidosis | Parent | USA |
| **Talha Zaidi** | Alpha Mannosidosis | | USA |