



4TH GLYCOPROTEINASES  
**INTERNATIONAL  
CONFERENCE**

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ADVANCES IN PATHOGENESIS AND THERAPY

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**JULY 23 - 26 2015**

ST. LOUIS, MISSOURI, UNITED STATES

**Program & Abstracts**



ISMRD would like to say A Very Special Thank You to the following organizations and companies who have very generously given donations and sponsorship to support the 4th International Conference on Glycoproteinases



THE PRENILLE  
FOUNDATION

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MARK HASKINS





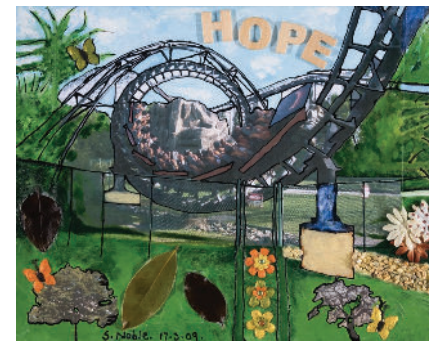
ISMRD is very proud to display 10 featured Expression of Hope artworks to be Auctioned at the Gala Dinner. These beautiful prints are from Genzyme's featured Artwork selection.



Sean Thomas Ackley, Philippines



Miriam Storchli, Switzerland



'Hope' by Sarah Noble, New Zealand



Sara DeAngelis, Russia



'All around the world' by Zih Yun Li, Taiwan



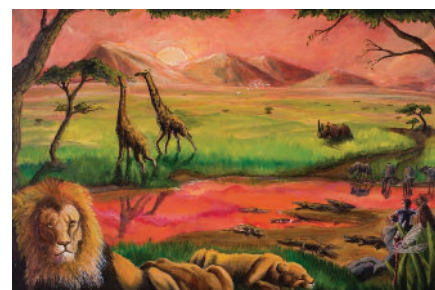
Gayle Rose, United States



Helen Walker, Australia



Naomi Arai, Japan



David Wentworth, Serbia



Nicklas Harkins, Canada

# Contents

Welcome	<b>1</b>
ISMRD Mission & Governance	<b>3</b>
ISMRD General Information	<b>5</b>
Scientific Program	<b>9</b>
Family Program for Mucopolipidosis	<b>11</b>
Family Program For Alpha Mannosidosis /Sialidosis/ Fucosidosis/Aspartylglucosaminuria	<b>13</b>
Childrens Program	<b>16</b>
Abstracts	<b>17</b>
Speaker Profiles	<b>60</b>
Delegates	<b>81</b>

## SCIENTIFIC COMMITTEE:

Stuart Kornfeld  
(Chair, Scientific Planning Committee)  
Steve Walkley  
Sara Cathey  
Richard Steet  
Alessandra d'Azzo

## FAMILY CONFERENCE COMMITTEE:

Jenny Noble (Conference Organiser)  
Jackie James (Conference Organiser - St. Louis)  
Mark Stark  
John Forman  
Susan Kester  
Carolyn Paisley-Dew  
Tish Adkins





# Welcome!

On behalf of ISRMD, I would like to welcome all of you to the Glycoproteinoses: Fourth International Conference on Advances in Pathogenesis and Therapy in St. Louis, Missouri. I know that the next few days will be a great opportunity for you to learn about advances in the understanding of the pathology and therapeutics for this group of extremely rare diseases; I also hope you will take the opportunity to meet with others who share your interest in finding therapies and cures for these devastating disorders. Since these conditions are so rare, there are no concentrations of researchers, clinicians, or patients anywhere in the world. I am extremely pleased that ISRMD is able to bring together this group of people from around the globe; it has been three years since the last conference, and I know you will be very excited to see how much progress has been made in understanding and treating these rare disorders.

It takes a lot of work and funding to bring together this great group of people. I would first like to thank our Primary Investigator, Dr. Stuart Kornfeld. We are so fortunate that he agreed to host this conference. Without him, this conference would simply not be possible. He has of course done a great job organizing fantastic speakers; but he has also done so much more to reach out to other organizations to participate and to fund this conference. I would also like to thank our corporate sponsors, who have contributed so much to this conference. I know

that it is the people at these organizations who make this happen. These people that support orphan disease research are not hoping for the next blockbuster drug; instead they are using their resources for the altruistic goal of helping children and families overcome these debilitating conditions. The same is true for the researchers and clinicians who spend time studying these diseases; and caring for the children affected by these disorders.

I would also like to thank the families who are part of this conference. As a father of a son with alpha-mannosidosis, I know how terrible it is to get a diagnosis of a rare metabolic disorder for your child. I know how alone you feel when you realize that your doctor has probably never heard of the disease, and there is no one else in your state or in your country to talk to about the disease. It is the banding together of these isolated families through the power of the internet, email, and social media that is the heart of ISRMD; and it is what has made this conference possible. Your donations of time and money, your commitment to help support research projects, and your relentless effort to help your children live fuller lives is the bedrock of our organization. I would encourage the families who have been with us for a while to reach out to the new families or those travelling from other countries. I know that lifelong friendships are made this way through the shared bond of caring for a special child.

It is our goal that we provide fun, supervised activities for your children so that you can get time to meet with other families. I would also encourage you to reach out to the researchers and clinicians attending this conference. I know from experience that they welcome the chance to meet with you.

As most of you know, ISRMD is an all-volunteer organization. We have no paid employees, and all work is done by our board. It takes a huge amount of work to pull this conference together. Led by Dr. Kornfeld, all of our board members have been working hard to get funding, organize the venue and travel, arrange children's activities, and make sure we are fed. All of our board members have contributed, but I would especially like to recognize Jenny Noble and Jackie James, who have worked tirelessly to make sure that this is a great experience for everyone.

Welcome to the Conference! I hope you learn something, have a great time, and meet new friends.

Thank you,

**Mark Stark,**  
*President*



On behalf of the Scientific Planning Committee, I want to extend a warm welcome to all the investigators and families who have traveled to St. Louis, in some cases from distant locations, to attend the Fourth International Conference on the Glycoproteinoses. The goal of the scientific program is to bring together leading investigators from around the world to discuss the latest advances in understanding the pathophysiology of these rare disorders and the status of the development of new therapies. The intent is to stimulate an interchange of ideas and develop collaborations among investigators with different approaches and expertise. Another goal is to increase the awareness of these underserved forms of lysosomal diseases among new investigators, post-doctorate fellows and graduate students. The conference is designed to foster interactions between the investigators and patients/affected families.

We hope that you have a rewarding experience at the meeting.

**Stuart Kornfeld, M.D.**  
*Chair, Scientific Planning Committee*





# 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 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



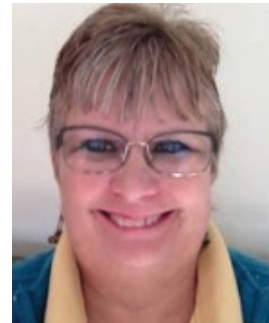
**Mark Stark**  
President United States



**Jenny Noble**  
Vice President/Admin  
New Zealand



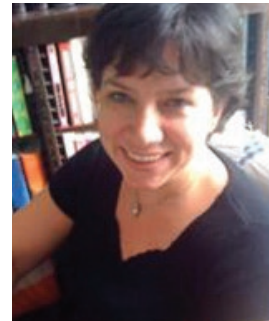
**John Forman**  
Vice President/Research  
New Zealand



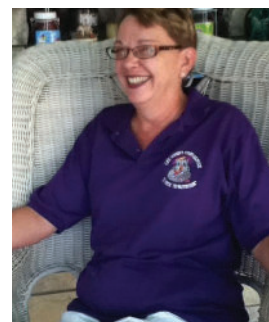
**Tish Adkins**  
United States



**Carolyn Paisley-Dew**  
Australia



**Jackie James**  
United States



**Susan Kester**  
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 Tromsøe,  
Norway



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



**Mark Haskins**, V.M.D., Ph.D.  
University of Pennsylvania Vet-  
erinary 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

Please see Jenny Noble or Mark Stark during Registration or the Welcome Reception on 23rd July to get your presentations loaded onto computers prior to the commencement of the conference.

If you missed the above please touch base with Jenny or Mark or your presentation chairperson 10-15 minutes prior to the commencement of the session.

## NAME TAGS

Name tags are to be worn at all times to allow entry into the meeting and social functions.

## TOUR OPTIONS FOR FAMILIES

Saturday 25th July  
The Science center  
History Museum  
Art Museum  
The Arch  
The Ballpark Village  
Downtown Shopping

## REGISTRATION DESK TIMES

Thursday 23rd July:  
4.30pm - 6:30pm

Friday 24th July:  
7:30am - 4:30pm

Saturday 25th July:  
8:00am - 12noon

Sunday 26th July:  
8:00am - 10:00am

## CATERING

Welcome Reception 23rd July  
Breakfast, Morning / Afternoon break and Lunch 24th July  
Breakfast, Morning Break and Gala Dinner Saturday 25th July  
Breakfast and Morning Break 26th July  
Breakfast will be available from 7.00am - 8.30am in the Grand Foyer

## 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

Thursday 23rd July

Time: 6.30pm – 8.30pm

Room: Lindberg Room

Don't miss a great opportunity to meet your colleagues, meet old friends and make new one's before the conference begins at 8.30am the next day. An evening of local food and wine not to be missed.

A cash bar will be available for all drinks during the Welcome Reception and the Gala Dinner.

## GALA DINNER

Saturday 25th July

Time: 6.30pm for seating at 7pm

Room: The Arch Ballroom

Join us for one of the highlights of our conference, this year's Gala Dinner will be something a little special. Pre-dinner drinks will be available at a cash bar before the commencement of a 3-course dinner. The food, wine and entertainment promise to give you a great night of fun and relaxation - and we have not forgotten the children - part way through the evening the children will step out the door and into a carnival atmosphere for some fun and entertainment of their own.

## PHOTOGRAPHER

ISMRD has arranged for a Photographer to be available from 4.30 - 6.30 to take family portraits.

If you would like to have a family photo taken please go to the registration desk and book a time.





# Memorial Service

Conference delegates are invited to join the ISMRD Board of Directors at the Ballpark Busch - II- Infield across the road from the Hotel for a memorial service in memory of all those who have passed away from Glycoprotein Storage Disorders.

Date: 24th July

Time: 12.50pm

Venue: Ballpark Busch - II- Infield

Dove Release: 1.10pm



Look for me in Rainbows  
Time for me to go now, I won't say good bye;  
Look for me in rainbows, way up in the sky.  
In the morning sunrise when all the world is new,  
Just look for me and love me, as you know I loved you.

Time for me to leave you, I won't say good bye;  
Look for me in rainbows, high up in the sky.  
In the evening sunset, when all the world is through,  
Just look for me and love me, and I'll be close to you.

It won't be forever, the day will come and then  
My loving arms will hold you, when we meet again.  
Time for us to part now, we won't say good bye;  
Look for me in rainbows, shining in the sky.  
Every waking moment, and all your whole life through  
Just look for me and love me, as you know I loved you.

Just wish me to be near you,  
And I'll be there with you.

Music and lyrics: Conn Bernard (1970), Vicki Brown







# Scientific Program

## DAY 1 : JULY 24, 2015

### A.M. – Session 1 Expanding Role of Lysosomes in Cell Function – Chair: Stuart Kornfeld

8:30 a.m	Welcome / Introduction to Meeting
8:45 a.m	Keynote: William Sly - USA
9:25 a.m	TFE3 Regulates Cellular Adaptation to Stress – Rosa Puertollano - USA
9:50 a.m	Harnessing the Autophagy-Lysosomal Biogenesis Response in Macrophages to Treat Atherosclerosis – Babak Razani - USA
10:15 a.m	Break
10:35 a.m	Chaperone-Mediated Autophagy – Ana Maria Cuervo - USA
11:00 a.m	Lysosome-Mediated Cell Death – Karin Ollinger - Sweden
11:25 a.m	Lysosome-Initiated Neuronal Cell Injury in the Glycoproteinoses and other Storage Diseases – Steve Walkley - USA
11:50 a.m	Lunch
12:50 p.m	<b>Memorial Service</b> – The ISMRD board would like to invite you all to join us in the Ballpark Busch - II- Infield across the road from the hotel to attend a short memorial service and dove release in memory of all those who have lost their battles with these very rare diseases.

### P.M. – Session 2 $\alpha$ -Mannosidosis / Sialidosis / Aspartylglycosaminuria / Fucosidosis – Chair: Steve Walkley

1:15 p.m	The Natural course and complications of Alpha-Mannosidosis - A retrospective and descriptive study – Dag Malm - Norway
1:40 p.m	Characterisation of A-Mannosidase Mutations – How Many Things Can Go Wrong – Pirkko Heikinheimo - Finland
2:05 p.m	Pathogenic Cascades downstream of excessive Lysosomal Exocytosis in Sialidosis – Alessandra d'Azzo - USA
2:30 p.m	Break
2:50 p.m	Insights from AGU null mice – Steven Gray - USA
3:15 p.m	Evaluation of responses to therapy in canine Fucosidosis – Rosanne Taylor - Australia
3:40 p.m	Recombinant Human Protective Protein/ Cathespin A: An update of an Enzyme Replacement Therapy for Galactosialidosis – Vish Koppaka - Ultragenyx Pharmaceuticals
3:52 p.m	Analysis of Urinary Free Oligosaccharides for the Diagnosis of Glycoproteinoses using UPLC-SRM – Laura Pollard - Greenwood Genetic Center- USA
4:04 p.m	Clinical and Biochemical Characterization of a Rare Case of Beta-Mannosidosis – Katrina Simmons - Greenwood Genetic Center- USA
4:16 p.m	Revisiting Aspartylglucosaminuria: Characterization of structural consequences of novel and old mutations reveals novel prospects for therapy – Ritva Tikkanen - Germany

## DAY 2: JULY 25, 2015

### A.M. – Session 3 New Insights Into ML II / ML III – Chair: Alessandra d'Azzo

8:30 a.m	Natural History of (Still Untreated) Mucopolidosis II and III – Sara Cathey - USA
8:55 a.m	Characterization of Ptase $\alpha/\beta$ & $\gamma$ Mutations – Stuart Kornfeld - USA
9:20 a.m	Pathogenic alterations in the Brain, Bones and Immune system of ML II Mice – Thomas Braulke - Germany
9:45 a.m	Break
10:05 a.m	Extracellular Cathepsin Proteases contribute to ML III Pathogenesis: Insights from Zebrafish Hearts and Bones – Heather Flanagan-Steet - USA
10:30 a.m	Stuttering & the M6P Pathway – Terra Barnes - USA
10:55 a.m	Analysis of ML II Patient Mutations Revealed Structural requirements of the GlcNAc-1-phosphotransferase Complex for ER exit, proteolytic activation and enzymatic activity – Raffaella DePace - Germany
11:07 a.m	Humoral Immune Reponse is not Altered in Brazilian Patients with Mucopolidosis III Gamma – Taciane Alegra - Brazil
11:19 a.m	Mannose 6-phosphate-independent Transport Mechanisms to Lysosomes – Sandra Markmann - Germany

**Tours for Professional Delegates:** Please assemble in the Hotel Foyer at 12.15pm.

**The Arch:** For delegates heading the the Arch this is a short walk down town - You may all like to go together.

**For the Zoo, Art, Museum and Gardens**, the Bus departs the hotel at 12.30pm and will drop you off in the following order

1. Zoo
2. Art Museum
3. The Botanical Garden

The Bus will pick you up in the following order to return to the hotel.

1. The Garden at 4.15pm
2. The Zoo at 4.35pm (Art museum people could you walk over to the zoo for pick up.

### 12:00 p.m Afternoon free for those not joining the Tours

6:00 p.m -	Gala Dinner in The Arch View Ballroom - Cash bar available for all drinks.
7:00 p.m -	Seating

## DAY 3: JULY 26, 2015

### A.M. – Session 4 New Approaches to Therapy – Chair: Sara Cathey

8:30 a.m	Central Nervous System-Directed Gene Therapy For Mucopolysaccharidosis VII – Kathy Ponder - USA
8:55 a.m	Intracerebrospinal fluid AAV-mediated gene therapy for MPSIII – Fatima Bosch - Spain
9:20 a.m	Hematopoietic stem cell based gene therapy for the treatment of lysosomal storage disorders – Alessandra Biffi - Italy
9:45 a.m	Break
10:05 a.m	A Journey from maturing RBC and Platelets to crossing the Blood Brain Barrier for treatment of CNS deficits in MPS 1 Mice – Dao Pan - USA
10:30 a.m	Chaperone-mediated Gene Therapy for Type I Sialidosis – Ida Annunziata - USA
10:55 a.m	Pharmacological Chaperoning in Fabry and Schindler Diseases – Scott Garman - USA
11:20 a.m	Chorid Plexus-directed Viral Gene Therapy for Alpha-Mannosidosis, a Prototypical Lysosomal Storage Disease – Eun-Young Choi - NICHD
11:32 a.m	Identification of the Amino Acids Inserted during Nonsense Suppression and their Functional Consequences in a Cystic Fibrosis Model – David Bedwell - USA
11:44 a.m	Meeting Summary – Richard Steet - USA



# Family Program for Mucopolidosis

We have two workshops happening at different times, which will see you attend various parts of the Scientific Program with a break out session that will break the science down to lay terms and then the next day there will be a workshop specifically for your particular disorders.

## DAY 1 : JULY 24, 2015

### Families to join the Scientific Program for Welcome and Keynote Presentation

8:30 a.m. Welcome / Introduction to Meeting

8:45 a.m. Keynote: **William Sly - USA**

### Families move out to attend Family meeting

9:25 a.m. ISMRD the Organization - The development of the organization and its achievement – **Mark Stark - USA**

9:50 a.m. ISMRD - Its future plans and goals – **Jackie James - USA**

10:15 a.m. Break

### New Horizons in Research and Therapies for Glycoproteinoses

10:35 a.m. Research - Where are we up to and where are we going? – **Mark Haskins - USA**

11:00 a.m. Current and Future Therapies – **Marc Patterson - USA**

11:25 a.m. Rare Trait Research group for Aspartylglucosaminuria – **Julia Taravella - USA**

11.50 a.m. Questions and Answers

12:00 p.m. Lunch

12:50 p.m. **Memorial Service** – The ISMRD board would like to invite you all to join us in the Ballpark Busch - II- Infield across the road from the hotel to attend a short memorial service and dove release in memory of all those who have lost their battles with these very rare diseases.

### Workshop Mucopolidosis: Clinical Management

1:15 p.m. Overview of Mucopolidosis and its issues – **Jules Leroy - Belgium**

1:35 p.m. Surgical management of Cervical, Thoracic and Lumbar spine – **Michael Kelly - USA**

1:55 p.m. Upper Limb management in Mucopolidosis – **Richard Morbey - New Zealand**

2:15 p.m. Break

2:35 p.m. Potential therapies for arresting bone resorption in Mucopolidosis – **Michael Whyte - USA**

3:25 p.m. Cardiac issues - what are the issues / what to do – **Nick Pietris - USA**

3:50 p.m. Schooling issues/special education/IEPs – **Lucia Horowitz - USA**

4:15 p.m. OCD - What is it? Can we treat it? Tips for parents – **AmyRuth Bartlett - USA**

5:00 p.m. Close of day



## DAY 2: JULY 25, 2015

A.M. – **Session 3 New Insights Into ML II / ML III** – Chair: **Alessandra d'Azzo**

Mucopolidosis Families to Join Scientific Program

8:30 a.m. Natural History of (Still Untreated) Mucopolidosis II and III – **Sara Cathey - USA**

8:55 a.m. Characterization of Ptase  $\alpha/\beta$  &  $\gamma$  Mutations – **Stuart Kornfeld - USA**

9:20 a.m. Pathogenic alterations in the Brain, Bones and Immune system of ML II Mice – **Thomas Bräulke - Germany**

9:45 a.m. Break

10:05 a.m. Extracellular Cathepsin Proteases Contribute to MLII Pathogenesis: Insights from Zebrafish Hearts and Bones – **Heather Flanagan-Steet - USA**

10:30 a.m. Stuttering & the M6P Pathway – **Terra Barnes - USA**

10:55 a.m. ML Families please break out and go to Market Street Room for scientific break down – **Richard Steet - USA**

12:00 p.m. Close of day – Everyone on their own to go out and explore St. Louis  
See conference book page 5 for sightseeing suggestions

6:00 p.m. - Gala Dinner in The Arch View Ballroom - Cash bar available for all drinks.

7:00 p.m. - Seating

## DAY 3: JULY 26, 2015

8.30am Families to join the Scientific program

11:20 a.m. Meeting summary and close



# Family Program

For Alpha Mannosidosis / Sialidosis / Fucosidosis / Aspartylglucosaminuria

We have two workshops happening at different times, which will see you attend various parts of the Scientific Program with a break out session that will break the science down to lay terms and then the next day there will be a workshop specifically for your particular disorders.

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### Families move out to attend Family meeting

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9:50 a.m. ISMRD - Its future plans and goals – Jackie James - USA

10:15 a.m. Break

10:35 a.m. Research - Where we have been, where we are, and where are we going? – Mark Haskins - USA

11:00 a.m. Current and Future Therapies – Marc Patterson - USA

11:25 a.m. Rare Trait Research group for AGU – Julia Taravella - USA

11:50 a.m. Questions and Answers

12:00 p.m. Lunch – please join the scientific conference after lunch for presentations on your disorders

12:50 p.m. **Memorial Service** – The ISMRD board would like to invite you all to join us in the Ballpark Busch - II- Infield across the road from the hotel to attend a short memorial service and dove release in memory of all those who have lost their battles with these very rare diseases.

### P.M. – Session 2 $\alpha$ -Mannosidosis / Sialidosis / Aspartylglycosaminuria / Fucosidosis

1:15 p.m. The Natural course and complications of Alpha-Mannosidosis - A retrospective and descriptive study – Dag Malm - Norway

1:40 p.m. Characterization of A-Mannosidase Mutations – How Many Things Can Go Wrong – Pirkko Heikinheimo - Finland

2:05 p.m. Pathogenic Cascades downstream of excessive Lysosomal Exocytosis in Sialidosis – Alessandra d'Azzo - USA

2:30 p.m. Break

2:50 p.m. Insights from AGU null mice – Steven Gray - USA

3:15 p.m. Evaluation of responses to therapy in canine Fucosidosis – Rosanne Taylor - Australia

Please break off and go to Market Street Room for a break down of Scientific program

3:50 p.m. A.Mann/Sialidosis/Fucosidosis families please break out for Scientific break down – Richard Steet - USA

5:00 p.m. Close of day – Everyone on their own for the evening.

## DAY 2: JULY 25, 2015

### Workshop: A. Mann/Sialidosis/Fucosidosis/Aspartylglucosaminuria

8:30 a.m. Overview Neurological Implications – Marc Patterson - USA

9:15 a.m. Fucosidosis - Present Knowledge and Future Prospects – Michael Beck - Germany

9:45 a.m. Break

10:05 a.m. Hematopoietic Cell Transplant for Glycoproteinoses – Troy Lund - USA

10:30 a.m. New Horizons in the development of therapies for Glycoproteinoses – Alessandra d'Azzo - USA

10:55 a.m. Schooling issues/Special Education/ IEPs – Lucia Horowitz - USA

11:00 a.m. Open discussion with presenters

12:00 p.m. Close of day - Everyone on their own to go out and explore St. Louis. See conference book page 5 for sightseeing suggestions

6:00 p.m. - Gala Dinner in The Arch View Ballroom - Cash bar available for all drinks.

7:00 p.m. - Seating

## DAY 3: JULY 26, 2015

8.30am Families to join the Scientific Program

11:20 a.m. Meeting summary and close





**IMPORTANT NOTICES FOR PARENTS**

Parents are requested to have their children at the assembly point at the hotel near registration. Look out for the colored balloons. Assembly time is 8am.

It is important to ensure that you are on time on day one, as it takes time to meet your carer and get the children transferred onto buses.

Please make sure that your child has on the conference tee shirt and cap, name tag and that they have all their personal needs for the day eg spare nappies/diapers, sunscreen, spare clothes.

If your child is in a stroller or wheelchair please show your carer how to fold and unfold the chair.

Please go to the Registration desk and check in each day.

The Zoo will be providing lunch for the children. Additional snacks and drinks will be in their backpacks.

For children on special diets please make sure you include this in their packs. If the hotel is providing a special meal e.g. gluten free please make sure we have provided that before you leave the hotel.

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.



**Children's Program**

Parents are requested to have their children at the assembly point at 8am sharp.

**DAY 1 : JULY 24, 2015 – ON SITE PROGRAM**

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

- 7:30 a.m Meet your caregivers and give all care instructions to the careworkers.
- 8:15 a.m Board the bus for the Zoo
- 10:30 Morning Break
- 11:30 p.m Lunch is being provided in the Rivers Edge Classrooms
- 3:00 p.m Board buses to return to the hotel
- 5:00 pm Parents to meet their children

**DAY 2: JULY 25, 2015**

- 8:00am All children to go to the childcare room
- 8.30am – 12.00pm Art therapist and story telling
- Girls 15 years and older please break off and go to Broadway 1 for some pampering.
- 10:00am – 12:00pm Hair, Makeup and Nails AND Posh morning tea donated by the London Tea room.
- Boys 15 years and older please break off with your carers and meet at Registration
- 9:00am Tour of St. Louis Cardinals Baseball Stadium. After the tour head to the Ballpark Village for a coke, snack etc.
- 11:45pm Return to the hotel
- 6.00pm for 7:00pm Get dressed up in your best clothes and join your families for our Gala Dinner and more entertainment

**DAY 3: JULY 26, 2015**

- 8.30am – 12.00pm All children to go to the childcare room
- 10:00am You will be visited by Darth Vader and his friends



# Abstracts

## RECEPTOR-TARGETED ENZYME THERAPY FOR MPS VII (SLY SYNDROME) - THE LONG JOURNEY FROM BENCH TO BEDSIDE.

WILLIAM SLY, M.D.  
St. Louis University, MO

Mucopolysaccharidosis type VII (MPS VII) is a rare, inherited (autosomal recessive) lysosomal storage disease affecting most organ systems in the body. The first case was reported in 1973. Well over 100 patients have since been identified. Its cause is a defect in glycosaminoglycan (GAG) breakdown due to deficiency of the enzyme beta-glucuronidase (GUS). Accumulation of undegraded GAGs and their secondary consequences lead to a multi-systemic disorder with hepatosplenomegaly, widespread skeletal abnormalities (dysostosis multiplex), joint deformities, hernias, cardiovascular abnormalities, cognitive defects, respiratory functional impairment, and shortened life span. Many affected patients present with gestational or perinatal non-immune hydrops fetalis. Studies on fibroblasts from the original patient in the late 1970's led to discovery of the mannose 6-phosphate receptor-mediated transport pathway by which most acid hydrolases are targeted to lysosomes. Studies of the fate of infused non-phosphorylated forms of

the enzymes helped identify the mannose receptor on macrophages that was the target of successful enzyme replacement in Gaucher Disease. The rarity of MPS VII patients and the wide variability in clinical severity delayed studies of experimental therapies in MPS VII. However, the MPS VII mouse was discovered at The Jackson Laboratory by Ed Birkenmeier in 1984 and became widely used for studies of therapy by hematopoietic stem cell transplantation, gene therapy, and enzyme replacement therapy. Notably, infusions of purified human GUS reduced storage, improved the course of the disease, and extended life span in the mouse model of MPS VII. These and other favorable pre-clinical trials in animals led regulatory agencies to approve a small Phase 1/2 clinical trial of enzyme therapy with recombinant hGUS for MPS VII patients in the UK in 2014. A Phase 3 study on 12 patients is now underway in the USA. Thus, there is hope for therapy after 40 years. Fingers crossed!

JULY 24, 2015

Scientific Program

8.45 a.m



## TFE3 REGULATES CELLULAR ADAPTATION TO STRESS

ROSA PUERTOLLANO, NIH/NHLBI, PH.D.

The discovery that expression of lysosomal genes is not constitutive but changes in response to nutrient status revealed that cells monitor lysosomal function and respond to degradation requirements and environmental conditions. TFEB was the first reported transcription factor capable of promoting lysosomal biogenesis and autophagy in response to nutrient levels. Recently, we identified the transcription factor E3 (TFE3) as novel regulator of lysosomal formation and function. In fully fed cells, TFE3 is recruited to lysosomes by active Rag GTPases leading to TFE3 phosphorylation by mTORC1 and retention in the cytosol by interaction with 14-3-3. After starvation or lysosomal stress, TFE3 rapidly translocates to the nucleus and activates genes associated with autophagy and lysosomal biogenesis, a critical step for cell survival during starvation conditions. Over-expression of TFE3 results in increased autophagy and enhanced

lysosomal biogenesis, as evidenced by an increase in the number of lysosomes and lysosomal activity. In contrast, depletion of endogenous TFE3 entirely abolishes the cellular response to starvation, thus confirming the crucial role of TFE3 in nutrient sensing and energy metabolism. Finally, we present evidence that TFE3 is a novel and very promising therapeutic target for the treatment of Lysosomal Storage Disorders by showing that overexpressed TFE3 increases the abundance of the lysosomal calcium channel MCOLN1, triggers lysosomal exocytosis, and promotes efficient cellular clearance in cellular model of Pompe disease. Given the high level of expression of endogenous TFE3 in critical tissues, such as brain and muscle, the ability of TFE3 to induce cellular clearance is of potential clinical relevance.

JULY 24, 2015

Scientific Program

9.25 a.m





## HARNESSING THE AUTOPHAGY-LYSOSOMAL BIOGENESIS RESPONSE IN MACROPHAGES TO TREAT ATHEROSCLEROSIS

BABAK RAZANI, M.D. PH.D.

Washington University, St. Louis, MO

Recent reports of the proatherogenic phenotype of mice with a macrophage-specific autophagy deficiency have renewed interest in the role of the autophagy-lysosomal system in atherosclerosis. Lysosomes have the unique role of processing both exogenous material such as excess atherogenic lipids and endogenous cargo that includes dysfunctional proteins and organelles via autophagy. Previously we demonstrated that oxidized LDL and cholesterol crystals, two of the commonly encountered lipid species in the atherosclerotic plaque, create a profound lysosomal and autophagy dysfunction in cultured macrophages. Overexpression of TFEB, a transcription factor that is the only known master regulator of lysosomal and autophagy biogenesis, in macrophages initiates a robust prodegradative response including induction of lysosomal and autophagy genes. This in turn ameliorates several deleterious effects of the lipid-mediated dysfunction, namely the blunting of inflammasome activation, enhancing cholesterol efflux, and

accelerating the degradation of protein aggregates. Our in vitro data suggest that the induction of a lysosomal biogenesis program in macrophages can have atheroprotective effects. Indeed, myeloid-specific TFEB overexpression in mice significantly reduces atherosclerotic plaque burden as well as plaque complexity as gauged by reduced necrotic core and markers of apoptosis. Interestingly, this protection is autophagy-dependent since these TFEB-overexpressing mice on a background of myeloid-specific autophagy (ATG5)-deficiency no longer demonstrate plaque reduction. Mechanistically, this indicates that suppression of the inflammasome and enhancement of cholesterol efflux and protein aggregate removal is dependent on the TFEB-autophagy axis. Taken together, our data support the notion that harnessing the prodegradative response in macrophages via TFEB can be atheroprotective and provides the impetus to evaluate mechanisms by which macrophage lysosomal and autophagy biogenesis can be modulated therapeutically.

JULY 24, 2015

Scientific Program

9.50 a.m

## CHAPERONE-MEDIATED AUTOPHAGY

ANA MARIA CUERVO, M.D., PH.D.

Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY

Cells can perform autophagy through different pathways that differ in the mechanisms by which the components that are going to undergo degradation (cargo) are delivered from the cytosol to lysosomes. One of these types of autophagy is known as Chaperone-mediated autophagy (CMA) that selectively degrades in lysosomes a subset of cellular proteins all bearing a targeting motif in their sequence. Recognition of this motif by the cytosolic hsc70 mediates targeting of the substrate protein to the lysosomal membrane and its binding to the single span membrane protein LAMP-2A. Translocation of the substrate protein into the lysosomal lumen is achieved through a rather unique transport mechanism in which the translocation unit is dynamically assembled and disassembled in response to substrate availability. In this talk, I will summarize some of the recent findings on the regulation of this tight translocation system and on the signaling mechanism that contribute to activation of this selective form of autophagy.

I will summarize in this talk our recent efforts directed to perform a molecular dissection of the components that participate in CMA and at the same time gaining a better understanding

of the physiological relevance of this pathway and its connections with disease. We have recently identified some additional components at the lysosomal membrane that are key for the modulation of the translocation event and at the same time have identified the first intracellular signaling mechanism that contribute to modulate CMA activity. Taking advantage of different cellular and animal models with regulatable CMA, we have now identified that CMA contributes to the cellular response to at least four type of stresses, proteotoxicity, lipotoxicity, genotoxicity and nutritional stress. Using animals with tissue-specific compromise CMA we are also learning about the contribution of CMA to basic cellular functions such as the control of metabolism and organism energetics from liver. In this talk, I will discuss some of these new CMA functions and the contribution of this selective form of autophagy as a cellular anti-aging mechanism.

This work is supported by grants: NIH-AG-21904; NIH-AG-AG031782.

JULY 24, 2015

Scientific Program

10.35 a.m



## LYSOSOME-MEDIATED CELL DEATH

KARIN OLLINGER

Experimental Pathology, Department of Clinical and Experimental Medicine, Linköping University, Sweden.

Lysosomes are acidic organelles essential for degradation, signaling and cell homeostasis. In addition, they are able to fine-tune the cellular response to stress and damage and play a key role in regulation of cell death. The most studied executors of lysosome-mediated apoptosis are specific lysosomal proteases, cathepsins. A critical step in the cell death inducing process is lysosomal membrane permeabilization (LMP) resulting in release of cathepsins from the lysosomal lumen to the cytosol. The cathepsins are often mediating apoptosis signal upstream mitochondrial events and the proteolytic activation of the pro-apoptotic protein Bid has been identified as one possible mechanism of action. The regulatory mechanism of lysosomal stability is, however, poorly understood. It seems to be heavily dependent on the composition of the lysosomal membrane. The natural sphingolipid sphingosine exhibits lysosomotropic detergent ability and is an endogenous candidate for controlling lysosomal membrane permeabilization. Moreover, the lysosomal cholesterol content also modulates the membrane stability. In fibroblasts from Niemann-Pick disease type C (NPC), cholesterol transporting proteins are mutated, which cause massive cholesterol accumulation within the lysosomes. NPC-1 fibroblasts show reduced LMP

when exposed to lysosomotropic weak bases with apoptosis inducing ability. Reduction of the cholesterol content by treatment with methyl- $\beta$ -cyclodextrin sensitizes the NPC cells to a cell death-inducing stimuli. Furthermore, the stability of the lysosomal membrane could be controlled by lysosomal pH. During cell death, stability of the lysosomal membrane is dependent on the amount of LAMP-2 (lysosomal associated membrane protein-2) present in the membrane. LAMP-2 levels are controlled by cathepsin B activity, which in turn is dependent of acidic lysosomal pH for its function. Thus, increasing the lysosomal pH reduces enzyme activity within the organelle and augments membrane stability.

Lysosomal dysfunction contributes to diseases, such as lysosomal storage disorders, neurodegenerative disorders and cancer. To remove toxic deposits from cells and retard the progression of devastating neurodegenerative diseases, therapeutic approaches to enhance lysosomal degradation activity are desirable. Moreover, restoration of lysosomal acidification by therapeutic interventions could represent an efficient way to promote the degradation and clearance of accumulating macromolecules.

JULY 24, 2015

Scientific Program

11:00 a.m

## LYSOSOME-INITIATED NEURONAL CELL INJURY IN THE GLYCOPROTEINOSES AND OTHER STORAGE DISEASES

STEVEN WALKLEY, D.V.M., PH.D.

Dominick P. Purpura Department of Neuroscience, Rose F. Kennedy Intellectual and Developmental Disabilities Research Center, Albert Einstein College of Medicine, Bronx, New York USA

The Glycoproteinoses represent a subgroup of lysosomal disorders, which in total represent nearly 60 monogenic human diseases caused by deficits of proteins involved in normal function of the endosomal/lysosomal system. Lysosomal disease pathogenesis is characterized by complex cascades involving progressive dysfunction of various tissues and organs, particularly the nervous system. A growing volume of data suggests that the primary compromise in lysosomal function instigates a broad array of downstream consequences that involve not only mishandling and storage of the primary non-degraded substrate, but also other diverse consequences, many completely unexpected. These include secondary/tertiary storage of multiple substrates, perturbations in endosomal and autophagosomal processing, protein aggregate formation (sometimes including neurofibrillary tangles and Lewy bodies), altered intracellular signaling leading to ectopic dendrite growth, axonal transport defects/spheroid formation, and so on. While many such events are now documented, their relationships to each other and to the primary gene defect remain enigmatic. In spite of such serious cytopathological changes,

neuron death is typically not an immediate outcome; rather, neurons can survive for years, indeed decades, in spite of significant amounts of intracellular storage and its consequences. What ultimately kills neurons is not clearly understood, though in some cases it may be related to induction of lysosomal membrane permeability (LMP) followed by release of toxic compounds into the cytoplasm. Invariably, glial cells, in spite of their own metabolic compromise, join the downward spiraling disease cascade and in some cases may actively contribute to it. Remarkably, many lysosomal diseases even with diverse gene and metabolic pathway involvement nonetheless share similarities in downstream pathogenic features. Understanding these complex disease cascades in the brain and their relationship to one another likely will provide insight into the more common neurodegenerative diseases as well as provides a window on possible sites for therapeutic intervention.

JULY 24, 2015

Scientific Program

11.25 a.m





## THE NATURAL COURSE AND COMPLICATIONS OF ALPHA-MANNOSIDOSIS - A RETROSPECTIVE AND DESCRIPTIVE STUDY

DAG MALM, M.D., PH.D.

Hilde Monica Frostad Riise Stensland, Øyvind Edvardsen, and Øivind Nilssen

Tromsø Centre of Internal Medicine (TIS as), 9008, Tromsø, Norway. Department of Medical Genetics, Division of Child and Adolescent Health, University Hospital of North Norway, 9038, Tromsø, Norway. 3Department of academic affairs, Aalesund University College, 6009, Aalesund, Norway. Department of Clinical Medicine – Medical Genetics, University of Tromsø, 9037, Tromsø, Norway

Most alpha-mannosidosis patients described have been children and information on the natural course of the disorder has been based on a very limited number of observations. In order to assess the disease presentation in detail and to study disease characteristics, a study was started in 1991 and has been ongoing for over 20 years. Patients with confirmed alpha-mannosidosis were recruited through The International Society for Mannosidosis and Related Diseases (ISMRD) where families affected with alpha-mannosidosis received a questionnaire on general clinical information to be filled out by the attending physician. The questionnaire was returned by 125 patients (64%). Of these, 45 patients were 15 years old or older at the time of evaluation. The questionnaire allowed us to assess the following features: Facial dysmorphism, columnar disease, arthritis, myopathy, hearing impairment mental impairment, psychosis, bone disease and motor function as well as general health.

In this prospective and descriptive study, the frequency and dynamics of clinical features and complications in alpha-mannosidosis. Normal features or absence of complications were expressed as – (minus), whereas various degree of features/ complications were expressed as +, ++ or +++ (plus), respectively. To depict eventual disease progression, the patients were age grouped in decades. Results are expressed in percentage within the respectable age group. The number of observations is given.

This study describes the progression of alpha-mannosidosis and may be helpful in determining the baseline for efficacy assessments of potential therapies.

JULY 24, 2015

Scientific Program

1.15 p.m

## CHARACTERISATION OF A-MANNOSIDASE MUTATIONS - HOW MANY THINGS CAN GO WRONG

PIRKKO HEIKINHEIMO

Department of Biochemistry, FI-20014 University of Turku, Finland

A-mannosidosis is a lysosomal storage disorder caused by mutations in the MAN2B1 gene. In order to understand the molecular aetiology of  $\alpha$ -mannosidosis we analysed the impact of individual MAN2B1 mutations on cell biology and the three dimensional structure of the human MAN2B1. We categorise the MAN2B1 missense mutations into four different groups based on their intracellular processing, transport and secretion in cell culture. Impaired transport to the lysosomes is a frequent cause of pathogenicity and correlates with a lack of protein processing. Mutant MAN2B1 proteins that find their way to the lysosomes are processed, but less efficiently than the wild types. The described four categories of missense mutations likely also represent different steps in the pathogenic cascade.

A general structural analysis on a set of lysosomal proteins demonstrates that severity of individual mutations cannot be determined based on their

position in sequence. Pathogenic mutations cluster into amino acids, which have an important structural role, which affect folding of the enzyme, or maintain covalent links between individual domains of the structure. A few amino acid types tolerate mutations well, unless the affected amino acid is in the active site area. Generally tolerated mutations include surface residues and changes without drastic alteration of residue volume. Most difficult mutations cause severe protein folding defects, or truncated target proteins.

Understanding the molecular mechanism of disease-associated mutations, and the difference between benign and deleterious mutations, helps to predict the significance of novel mutations. Potency of the treatments is also strongly dependent on the type of the individual disease associated mutations.

JULY 24, 2015

Scientific Program

1:40 p.m



## PATHOGENIC CASCADES DOWNSTREAM OF EXCESSIVE LYSOSOMAL EXOCYTOSIS IN SIALIDOSIS

ALESSANDRA D'AZZO, PH.D.

Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN, USA

Sialidosis (mucopolipidosis I) is a neurodegenerative glycoprotein storage disease caused by deficiency of the lysosomal sialidase NEU1. This enzyme regulates the catabolism of sialo-glycoconjugates by removing their terminal sialic acid residues. The complex phenotypes associated with sialidosis predict a spectrum of deregulated pathways downstream of NEU1 deficiency and accumulation of over-sialylated substrates, which are likely cell- and tissue-specific. Using Neu1<sup>-/-</sup> mice, a preclinical model of sialidosis, we have unraveled mechanisms of pathogenesis that have broadened our understanding of the physiological roles of NEU1 and revealed its involvement in more common adult pathological conditions.

We found that NEU1 functions as negative regulator of lysosomal exocytosis. By cleaving the sialic acids on LAMP1, NEU1 controls the number of lysosomes that traffic to and dock at the PM prior to fusing with the PM and releasing their contents extracellularly. In Neu1<sup>-/-</sup> cells an increased number of lysosomes marked with an over-sialylated LAMP1 dock at the PM and engage in lysosomal exocytosis. The ensuing exacerbation of this process has disastrous effects on PM and ECM integrity, and ultimately results in loss of tissue

homeostasis. This sequel is evident in the brain of the mutant mice, where excessive lysosomal exocytosis by hippocampal neurons is responsible for the progressive formation of  $\beta$ -amyloid deposits, resembling those in Alzheimer's disease (AD). We linked this pathogenic process to two synergistic events: i) lysosomal accumulation of over-sialylated APP, a novel substrate of Neu1, followed by its aberrant processing into toxic A $\beta$  peptides; ii) increased lysosomal exocytosis of amyloidogenic A $\beta$  into the brain parenchyma, the CSF and interstitial fluid. Furthermore, we demonstrated that Neu1 downregulation in 5XFAD mice, an established model of AD, accelerates the amyloidogenic process, while cerebral injection of NEU1 in the same model substantially reduces  $\beta$ -amyloid plaques. Thus, the sialidosis mice represent a spontaneously occurring model of early-onset AD, suggesting that NEU1 deficiency/downregulation is a risk factor for the development of the disease. These findings identify a previously unknown pathway for the secretion of A $\beta$  and define NEU1 as a potential therapeutic molecule for AD.

This study was supported in part by NIH grant GM060950, the Assisi Foundation of Memphis and ALSAC of St. Jude Children's Research Hospital

JULY 24, 2015

Scientific Program

2.05 p.m

## INSIGHTS FROM AGU NULL MICE

STEVEN GRAY, PH.D.

Gene Therapy Center, University of North Carolina, Chapel Hill, NC USA

AGU (OMIM #208400) is an autosomal recessive LSD caused by the absence of functional AGA protein, encoded by the AGA gene. It is considered a severe and progressive neurological disorder causing mental retardation along with some peripheral symptoms such as skeletal and joint abnormalities. Patients have slowed mental development throughout childhood, then regress around the 3rd decade of life to become severely impaired mentally and physically, highly dependent on supportive care thereafter. AGU patients have a median lifespan of approximately 50 years. There is a very low incidence of AGU worldwide, but there is a founder effect in Finland with a carrier prevalence of approximately 1:30. This places AGU as the 3rd most prevalent form of inherited mental retardation in Finland.

Previous studies explored three therapeutic options to treat AGU. The first, bone marrow transplant, was shown to be largely ineffective in human patients. The second option, enzyme replacement therapy, is somewhat promising in the mouse model of AGU but has been hampered by the inability of the AGA enzyme to cross the blood-brain-barrier. The third therapeutic option is gene therapy. AGA gene transfer was shown to be effective in early proof-of-concept studies over a decade ago, but at the time the technology was insufficiently developed to explore possible human translation.

Our laboratory has explored methods to use adeno-associated virus (AAV) vectors to broadly deliver therapeutic genes to the nervous system, primarily by intravenous or intrathecal injection of AAV9 vectors. Utilizing this technology, we have initiated a Phase I clinical trial for Giant Axonal Neuropathy (NCT02362438), in collaboration with the NIH Clinical Center. These approaches are being tested now for efficacy in the AGA knockout mice, and preliminary results of these ongoing studies will be discussed.

To better assess the utility of the AGA knockout mouse model to conduct preclinical studies, we undertook a longitudinal behavioral phenotyping study on a cohort of untreated mice (N=12 per sex and genotype). No significant genotype effects on body weight were seen up to 16 months of age. Significant hyperactivity, as well as reduced motor function (rotarod test), emerged at 14 months of age. Modest but significant deficits in spacial learning were apparent at 15 months of age. Survival is highly variable, but thus far consistent with the median lifespan of 20 months reported previously for this model. Overall, the AGA knockout mouse model appears to have a phenotype consistent with the human disease, and several relevant outcome measures are available to evaluate the efficacy of potential treatment.

JULY 24, 2015

Scientific Program

2:50 p.m





## EVALUATION OF RESPONSES TO THERAPY IN CANINE FUCOSIDOSIS

ROSANNE TAYLOR, PH.D.  
University of Sydney, Australia

Canine fucosidosis is a model for investigation of the neurodegenerative processes and responses to therapy in this rare human glycoproteinosis. Fucosidosis is a spontaneous disease of English Springer Spaniels caused by alpha-L-fucosidase deficiency, with accumulation of glycoasparagines and progressive clinical signs of diffuse neurological disease, failure to thrive and reproductive abnormalities. Recent studies have shown the canine neural pathology commences before 2 months of age with early vacuolation and perivascular storage, neuronal loss, astrocytosis, myelin loss, microgliosis and axonal spheroid formation throughout the central nervous system by 4 months age, well in advance of clinical signs of motor dysfunction. Neuroinflammation is major contributor to progressive pathology, while hypomyelination occurs early and is the primary cause of early myelin loss. Apoptotic cell death is triggered through death receptor and mitochondrial-mediated pathways. Novel biomarkers of inflammation, the chemoattractant proteins KC/CXCL1 and MCP-1/CCL2, can be monitored in cerebrospinal fluid during treatment. Once clinical signs of ataxia commence at 8-12 months of age significant, likely irreversible structural changes in the brain parenchyma commence, which progress to death or euthanasia by 36 months of age.

Treatments tested in this model showed best responses to bone marrow transplantation prior to 6 months age, limited response from 6-12 months

and very little impact from 12 months onwards. Enzyme replacement delivered by repeated intravenous injection in the first year of life had little if any impact with no detectable enzyme reaching brain tissue. Repeated intracisternal injection of enzyme from 2-4 months age achieved low, variable enzyme levels and substrate reduction in neural tissue. This delayed the progress of vacuolation and reduced substrate accumulation in neural tissue but did not halt demyelination, neuron loss or spheroid formation.

Correlation of the pathological markers with the clinical signs of sensory, motor and behavioural dysfunction identified microgliosis and apoptotic cell death to be significant contributors to the severity of clinical dysfunction. Substantial, sustained enzyme replacement in neural tissue before 6-12 months age was a critical period for intervention in the dog to achieve clinical benefit. The neurological dysfunction score may provide a measure for monitoring treatment responses that correlates with pathological changes.

This presentation will review the development of early lesions in canine fucosidosis, describe markers of early disease progression and consider how these correlate with clinical signs. The effect of bone marrow transplantation and enzyme replacement therapy on canine fucosidosis will be reported.

JULY 24, 2015

Scientific Program

3.15 p.m

## RECOMBINANT HUMAN PROTECTIVE PROTEIN / CATHESPIN A: AN UPDATE OF AN ENZYME REPLACEMENT THERAPY FOR GALACTOSIALIDOSIS

VISH KOPPAKA

Ultragenyx Pharmaceutical Inc., Novato, CA, USA; 2Department of Genetics,  
St. Jude Children's Research Hospital, Memphis TN, USA

Galactosialidosis (GS) is a rare, autosomal, glycoprotein storage disease caused by a primary defect of the multifunctional lysosomal serine carboxypeptidase, Protective Protein/Cathepsin A (PPCA) and secondary deficiency of neuraminidase1 (NEU1) and  $\beta$ -galactosidase ( $\beta$ -GAL). The three enzymes form a high molecular weight lysosomal complex, and association with PPCA assures the proper compartmentalization, catalytic activation and stability of the two glycosidases. The severe deficiency of NEU1 in GS patients is the cause of the progressive accumulation of sialylated glycoproteins in tissues and body fluids.

Our ultimate aim with this development program is to restore PPCA in GS patients, using enzyme replacement therapy, thereby rescuing the activities of NEU1 and  $\beta$ -GAL, and reducing the detrimental buildup of oversialylated substrates in tissues and body fluids.

We have successfully developed a CHO cell line that overexpresses the recombinant human PPCA protein, and developed a reliable process for the purification of the recombinant 54 kDa zymogen from the culture medium. Preliminary

in vitro experiments have already demonstrated that the recombinant PPCA zymogen is taken up by deficient fibroblasts through the mannose-6-phosphate receptor pathway, and converted to the mature and active 32/20 kDa two-chain enzyme. Following PPCA uptake, we have also shown the subsequent rescue of NEU1 and  $\beta$ -GAL activities, which is a critical step towards demonstrating the potential effectiveness of the recombinant protein in correcting the disease.

The next step is a proof of concept study to verify the potency of PPCA and demonstrate the reversion of the phenotype in the GS mouse model. The GS mice will be treated with the recombinant PPCA, followed by evaluating the distribution of the protein in affected tissues, rescue of the NEU1 and  $\beta$ -GAL activities, and subsequent reduction in storage of substrate in target tissues. Additionally we will evaluate the toxicity of the recombinant human PPCA administration in the GS mice. The ultimate goal of our work is to develop an efficient and non-invasive therapy for the treatment of GS

JULY 24, 2015

Scientific Program

3.40 p.m



## ANALYSIS OF URINARY FREE OLIGOSACCHARIDES FOR THE DIAGNOSIS OF GLYCOPROTEINOSSES USING UPLC-SRM

LAURA POLLARD

Greenwood Genetic Center, Greenwood, SC

The glycoproteinoses are a subset of inherited lysosomal storage diseases (LSDs) that are caused by the deficiency of an enzyme responsible for the degradation of glycoproteins in the lysosome. The enzyme deficiency results in the accumulation of intermediate metabolites such as free oligosaccharides (FOS). Analysis of urinary FOS via thin layer chromatography is a common screening test used to identify patients with certain LSDs, including several glycoproteinoses; however its intrinsic limitations have driven the need for more sensitive and specific analytical methods. Recently, the combination of derivatization and mass spectrometry has shown great potential for the analysis of urinary FOS. Here, a method using ultra-high performance liquid chromatography (UPLC) and selected-reaction monitoring (SRM) was developed to create a specific LC fingerprint for various LSDs, including six glycoproteinoses. Urine samples were derivatized by butyl-4-aminobenzoate (BAB) using a modification of a previously reported method. Scheduled SRM was developed for targeted analysis of FOS from patient urine samples. Preliminary results show elevated FOS for each of eight LSDs including: Pompe disease (Hexose3-8),

Alpha-Mannosidosis (HexNAc1Hexose2-7), Beta-Mannosidosis (Man(β 1-4)GlcNAc), Fucosidosis (HexNAc1Hexose1Fucose1Neu5Ac1, HexNAc2Hexose3 Fucose1 and Hexose3Fucose2), GM1 Gangliosidosis (HexNAc2Hexose3, HexNAc2Hexose4, HexNAc3Hexose4 and HexNAc3Hexose5), and Sialidosis (HexNAc2Hexose3Neu5Ac1). A sample from a Galactosialidosis patient also had elevated HexNAc2Hexose3Neu5Ac1 but with higher abundance (approximately 12 fold higher). A series of elevated FOS was identified in urine from Mucopolipidosis II and III patients, including one or more FOS observed in each of the other disorders. Further development of a quantitative / semi-quantitative method is currently underway. The improved method would allow us to distinguish disorders with similar TIC patterns but different abundance (e.g. GM1-gangliosidosis vs. Sialidosis) and could provide biomarkers to assess the effectiveness of treatment. Preliminary results for a Beta-Mannosidosis patient demonstrate greater than 50% reduction in the disease-specific FOS post-bone marrow transplantation.

JULY 24, 2015

Scientific Program

3.52 p.m

## CLINICAL AND BIOCHEMICAL CHARACTERIZATION OF A RARE CASE OF BETA-MANNOSIDOSIS

KATRINA SIMMONS

Greenwood Genetic Center, Greenwood, SC. Greenwood Genetic Center, Charleston SC. University of Minnesota Medical School, Division of Blood and Marrow Transplant, Minneapolis, MN

Beta-mannosidosis (OMIM # #248510) is an autosomal recessive lysosomal storage disease caused by mutations in the *MANBA* gene. Only approximately 20 cases of beta-mannosidosis have been reported worldwide. Patients can present with demyelination, intellectual disability, developmental delay, frequent infections, speech impairment, deafness, and hypotonia. We have recently been involved in the diagnosis of a 4.5 year old male with beta-mannosidosis. The patient had normal growth parameters at birth with no congenital anomalies. By 9 months of age his head size dramatically increased, he was moderately hypotonic, and was diagnosed with global gross and fine motor delay. An initial MRI was performed at one year of age that found no structural abnormalities. A second MRI was performed at the age of four that discovered severe demyelination. Lysosomal enzyme testing revealed beta-mannosidase deficiency. Beta-mannosidase activity was deficient in leukocytes (2.62 nmol/hr/mg; normal 10 – 162.4), plasma

(0.1 nmol/hr/mL; normal 50-181), and dried blood spots (0.639 nmol/mL blood/hr; normal 13 – 71). Urine oligosaccharide analysis via thin layer chromatography was normal; however, tandem mass spectrometry revealed an abundance of a disaccharide associated with beta-mannosidosis. Sequencing of the *MANBA* gene revealed two heterozygous alterations: a previously reported frameshift mutation in exon 5 (c.563\_572dup10), which was inherited from the mother, and a novel missense variant in exon 12 (c.1499G>A, p.R500H), which was inherited from the father. The patient has recently received a bone marrow transplant and we will continue to monitor his enzyme levels.

JULY 24, 2015

Scientific Program

4.04 p.m





## REVISITING ASPARTYLGLUCOSAMINURIA: CHARACTERIZATION OF STRUCTURAL CONSEQUENCES OF NOVEL AND OLD MUTATIONS REVEALS NOVEL PROSPECTS FOR THERAPY

RITVA TIKKANEN

Institute of Biochemistry, Medical Faculty, University of Giessen, Friedrichstrasse 24, D-35392 Giessen, Germany

Aspartylglucosaminuria (AGU) is a recessive glycoprotein storage disorder that is caused by mutations in the gene for the lysosomal enzyme aspartylglucosaminidase (AGA). This enzyme is involved in glycoprotein degradation and cleaves the bond between asparagine and the carbohydrate. Missing AGA activity results in a progressive mental retardation of AGU patients from early childhood on, but the life expectancy is not severely compromised. AGU is most common in Finland, but an increasing number of AGU cases have recently been diagnosed elsewhere in the world. AGA is a heterotetrameric enzyme ( $\alpha\beta$ )<sub>2</sub> that is synthesized as a catalytically inactive, single-chain precursor molecule that is autocatalytically cleaved into the active form. Almost all AGU mutations reside outside of the active site of AGA, but they impair the proteolytic processing of the AGA precursor into the subunits. The structural consequences of only few AGU mutations have been dissected. The most common

disease mutation Cys163Ser, also called AGUFin, results in a loss of a disulfide bond, impairing the folding of AGA. However, in the case of many other mutations, the structural defects are not that evident. We have here characterized the consequences of some newly-identified AGU mutations and show that these mutations cause a local misfolding of AGA, which is sufficient to impair the processing into the active form. However, these mutant enzymes principally retain their capacity to be activated and are localized in lysosomes. Dimerization with the wildtype AGA results in normal processing of the mutant enzyme which then also shows enzyme activity. Our data thus suggest that these AGU mutations cause a local misfolding which can be reverted by providing a normally folded "folding aid". However, the correct folding of the mutant AGA may also be obtained by means of pharmacological chaperones, opening novel prospects for chaperone-mediated therapy for AGU.

JULY 24, 2015

Scientific Program

4.16 p.m

## NATURAL HISTORY OF (STILL UNTREATED) MUCOLIPIDOSIS II AND III

SARA CATHEY, M.D.

Greenwood Genetic Center, SC

A cohort of mucopolipidosis patients of various ages have been followed for approximately a decade. In that time the FDA has approved 5 compounds intended to treat other lysosomal diseases and has granted orphan drug status to several more. Mucopolipidosis II and III remain rare diseases with no approved treatments.

In the lab, in vitro studies of mutant genotypes teach us about the functional domains in the alpha and beta chains of the GNPT enzyme complex and deepen our understanding of the role of specific mutations in intracellular vesicular trafficking. In the clinic, patients and the doctors who treat them struggle to deal with the repercussions of the gene mutations. The assignment of ML II or ML III is ultimately less important to the patient than the consequences of their gene mutations. The direct and probably indirect impact on the quality and function of soft connective tissue may be best

explored in the longer surviving ML III patients. A plea is made to think outside the lysosome, to consider the ML patient's connective tissue, from joints to alveoli to heart valves, as a diseased organ.

How might these rare disease patients benefit from the lessons learned in the treatment of a common condition, postmenopausal osteoporosis? A call for collaborations with rheumatology, endocrinology, and pulmonology researchers is issued. Study of the molecular characteristics of soft connective tissue in ML II and III are needed in an adequately designed research protocol controlled at least for age and tissue type. While ML II, ML III, and Intermediate ML are clinically distinct, insights from one of the subtypes improves our understanding of the entire group. For the first time the changes (or lack thereof) in cognitive and adaptive functioning in ML patients will be presented.

JULY 25, 2015

Scientific Program

8:30 a.m



## CHARACTERIZATION OF PTASE $\alpha/\beta$ AND $\gamma$ MUTATIONS

STUART KORNFELD, M.D.

Washington University School of Medicine, St. Louis, Missouri

UDP-GlcNAc:lysosomal enzyme GlcNAc-1-phosphotransferase (Ptase) tags newly synthesized lysosomal enzymes with mannose 6-phosphate recognition markers which are required for their targeting to the endolysosomal system. Ptase is an  $\alpha_2\beta_2\gamma_2$  hexamer that is encoded by 2 genes: the GNPTAB gene encodes the  $\alpha$  and  $\beta$  subunits while the GNPTG gene encodes the  $\gamma$  subunit. Mutations in GNPTAB and GNPTG give rise to the lysosome storage disorders mucopolisaccharidosis II  $\alpha\beta$ , III  $\alpha\beta$  and III  $\gamma$ . We are focusing on the consequences of patient missense mutations in GNPTAB and GNPTG in order to understand (1) the nature of the harmful effects of the mutations (misfolding, loss of catalytic activity, etc.) and (2) to provide insight into the functions of the various protein domains of the subunits. Using a multifaceted approach, including in vitro enzyme assays along

with cell- and zebrafish-based studies, we have identified a role for the Notch repeat 1 domain and the DMAP interaction domain of the  $\alpha$  subunit and the mannose 6-phosphate receptor homology (MRH) domain and the DMAP interaction domain of the  $\gamma$  subunit in the efficient phosphorylation of lysosomal acid hydrolases. We have also confirmed that the catalytic function of the enzyme is mediated by the stealth domain. These studies demonstrate that the patient missense mutations exert their harmful effects at different stages in the folding, transport, proteolytic activation, catalytic function and retention of the enzyme in the Golgi. The findings advance the understanding of how Ptase is able to recognize and phosphorylate 60 different lysosomal acid hydrolases.

JULY 25, 2015

Scientific Program

8:55 a.m

## PATHOGENIC ALTERATIONS IN THE BRAIN, BONES AND IMMUNE SYSTEM OF MLII MICE

THOMAS BRAULKE, PH.D.

Department of Biochemistry, Children's Hospital, University Medical Center Hamburg-Eppendorf, Germany

To investigate pathomechanisms underlying mucopolisaccharidosis II (MLII)-a prerequisite to develop therapeutic approaches-we have analyzed mice carrying a mutation identified in an MLII patient. Biochemically these mice are characterized by the complete loss of phosphotransferase activity resulting in the absence of mannose 6-phosphate targeting signals on lysosomal enzymes, their cell and tissue-specific missorting, and accumulation of non-degraded storage material in lysosomes. These mice show a progressive neurodegeneration particularly affecting granular and Purkinje cells in the cerebellum accompanied with the formation of axonal spheroids, cerebellar demyelination processes, and activation of astroglial and microglial cells. Quantitative mass spectrometric analyses of storage material revealed an accumulation of fucosylated sugar chains, gangliosides and cholesterol, most likely caused by the loss of few distinct lysosomal enzymes.

Surprisingly, an increased number of bone resorbing osteoclasts combined with reduced activity of bone forming osteoblasts were found to be responsible for the low bone mass and the osteoporotic phenotype in MLII rather than increased activity of osteoclasts. This phenotype can be corrected

in MLII mice by anti-resorptive bisphosphonate treatment. In addition, we found that high amounts of the cytokine interleukin-6 (IL-6) are secreted by dysfunctional MLII osteoblasts, which plays a crucial role in the stimulated osteoclastogenesis in MLII, and might present a novel therapeutic target.

Since both antigen processing and presentation, as well as cytotoxic functions of immune cells depend on lysosomal proteases, we have examined whether these processes are affected in MLII. The absence of mannose 6-phosphate residues led to a significant loss of lysosomal cathepsin proteases in B cells, and subsequently to lysosomal dysfunction with accumulation of storage material, impaired antigen processing and presentation, and antibody production. In contrast, T cells and dendritic cells maintained higher lysosomal protease activities and central cell functions. Most importantly, low concentrations of total immunoglobulins were found in MLII patients, and the specific antibody response to vaccination was poor or not detectable, indicating that these should be regularly checked in MLII patients.

JULY 25, 2015

Scientific Program

9:20 a.m





## EXTRACELLULAR CATHEPSIN PROTEASES CONTRIBUTE TO MLII PATHOGENESIS: INSIGHTS FROM ZEBRAFISH HEARTS AND BONES

HEATHER FLANAGAN-STEET, PH.D.  
University of Georgia

Hypersecretion of a subset of acid hydrolases is a hallmark feature of mucopolidosis II (MLII). Inappropriate extracellular action of these hydrolases has been proposed to contribute to disease pathogenesis, but the mechanisms that connect hydrolase activity to disease phenotypes remain poorly understood. Using a zebrafish model of MLII we have linked extracellular cathepsin K activity to abnormal bone, cartilage, and cardiac development. Work in craniofacial cartilage demonstrated that Ctsk disrupts the balance of TGF $\beta$ -related signaling during chondrogenesis. Elevated TGF $\beta$  signaling and reduced BMP signaling maintains MLII chondrocytes and osteoblasts in an immature developmental state - causing a more cartilaginous immature bone. Importantly, reducing either cathepsin K activity or expression significantly improves both biochemical and

behavioral phenotypes of MLII chondrocytes and osteoblasts. Parallel work in the cardiac system demonstrated similar alterations in atrio-ventricular valve and myocardial morphogenesis. Like noted in craniofacial structures these defects stem from incomplete cellular differentiation, which also correlates with notable changes in cellular signaling. Importantly, reducing CtsK also significantly improved multiple aspects of MLII cardiac pathology, including activation of TGF $\beta$ -related signaling effectors, cellular differentiation, and tissue morphology. Together these studies provide new insight into the role of secreted cathepsin proteases during early aspects of MLII pathogenesis and highlight their potential impact on growth factor regulation during cartilage and cardiac morphogenesis.

JULY 25, 2015

Scientific Program

10:05 a.m

## STUTTERING AND THE M6P PATHWAY

TERRA BARNES  
Washington University, St. Louis, MO

Stuttering is a common speech disorder that has been linked to mutations in the lysosomal enzyme targeting pathway. We asked whether a missense mutation in the Gnptab (N-acetylglucosamine-1-phosphotransferase subunits alpha/beta) gene found in human stuttering causes vocal or other abnormalities in mice. Mice vocalize in many situations, in the ultrasonic range, high above what humans can hear. Using language-agnostic analyses that generalize across human speech and mouse vocalizations, we found mice carrying this mutation produced fewer vocalizations per unit time and had longer pauses between vocalizations compared to littermate controls. Using the same analyses we found that people who stutter exhibit highly similar abnormalities in their speech. Like humans, abnormalities in the mice were restricted to speech; Gnptab missense mice were similar to wild type mice on an extensive battery of non-vocal behaviors. These data show that mutations in the lysosomal enzyme targeting pathway produce similar, highly-specific effects in human speech and mouse vocalizations, and establish this mouse as an animal model for stuttering.

Coauthors: Terra D. Barnes, David Wozniak, Joanne Gutierrez, Tae-Un Han, Dennis Drayna, and Timothy E. Holy

JULY 25, 2015

Scientific Program

10:30 a.m



## ANALYSIS OF ML II PATIENT MUTATIONS REVEALED STRUCTURAL REQUIREMENTS OF THE GLCNAC-1-PHOSPHOTRANSFERASE COMPLEX FOR ER EXIT, PROTEOLYTIC ACTIVATION AND ENZYMATIC ACTIVITY

RAFFAELLA DEPACE

Section Biochemistry, Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany and Department of Genetics, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Mucopolipidosis II (MLII) is an autosomal-recessive lysosomal storage disease of childhood caused by GNPTAB mutations. GNPTAB encodes the  $\alpha/\beta$ -subunit precursor of membrane-bound GlcNAc-1-phosphotransferase that is synthesized in the endoplasmic reticulum (ER) and transported to the Golgi apparatus for proteolytic activation by site-1 protease (S1P). The GlcNAc-1-phosphotransferase complex catalyzes the first step in the formation of mannose 6-phosphate targeting signals on soluble lysosomal enzymes required for their efficient transport to lysosomes. MLII is biochemically characterized by missorting of lysosomal enzymes and the accumulation of non-degraded material in lysosomes.

By comprehensive expression studies we have analyzed the impact of GNPTAB mutations identified in MLII patients on stability, transport from the ER to the Golgi apparatus, proteolytic S1P-mediated activation of the  $\alpha/\beta$ -subunit precursor and enzymatic activity of the GlcNAc-1-phosphotransferase. Frameshift and non-sense

mutations result in the retention of C-terminally truncated and enzymatically inactive  $\alpha/\beta$ -subunit precursor proteins in the ER due to the loss of cytosolic ER exit motifs. Surprisingly, also luminal missense mutations in highly conserved stealth 2 region in the  $\beta$ -subunit led to retention in the ER and loss of catalytic activity. Substitution of further conserved residues in this domain resulted in similar effects, suggesting a putative binding site for accessory proteins required for ER exit of  $\alpha/\beta$ -subunit precursors. Interestingly, a mutant  $\alpha/\beta$ -subunit precursor lacking 36 amino acids in the N-terminal part of the  $\beta$ -subunit showed partial Golgi localization, formation of abnormal  $\beta$ -subunits generated by S1P, and loss of activity.

Our data extend the knowledge about the structural requirements for GlcNAc-1-phosphotransferase activity and contribute to understanding of the clinical phenotype of MLII patients.

## HUMORAL IMMUNE RESPONSE IS NOT ALTERED IN BRAZILIAN PATIENTS WITH MUCOLIPIDOSIS III GAMMA

TACIANE ALEGRA

Hospital de Clinicas de Porto Alegre, Brazil

Mucopolipidosis (ML) II, ML III alpha/beta and ML III gamma are rare lysosomal diseases caused by GlcNAc-1-phosphotransferase deficiencies, and mutations in the GNPTAB and GNPTG genes. This enzyme is involved in the synthesis of the mannose 6-phosphate (M6P) marker, responsible for the targeting of lysosomal enzymes to lysosomes. It has been reported that total M6P deficiency impairs serum immunoglobulin levels and antibody responses to vaccination in MLII patients due to critical role of M6P-dependent transport routes for B cell functions and humoral immunity. Objectives: To characterize immune response of Brazilian ML III gamma patients. Methods: Cross-sectional study, including 3 ML III gamma patients seen at a National Reference Center for lysosomal diseases. Total IgA, IgM, IgG, IgE, leukocytes and lymphocytes levels, as well protein electrophoresis and antibodies against Rubella were evaluated. Results: One

female and two male siblings with MLIII (ages 19, 45 and 47 years, respectively) were included in this study. There was no history of recurrent infections. Leukocytes and lymphocytes levels were normal in all patients. The mean levels of IgA level was 231.67mg/dL (range 175-306; normal: 70-400), of IgE, 70.1 U/mL (range 30-116; normal: <100), of IgG 1413.3 mg/dL (range 1214-1690; normal: 700-1600), of IgM, 126.3 mg/dL (range 84-168; normal: 40-2030). All patients have been previously vaccinated against Rubella, and the mean IgG levels against Rubella was 310.5 U/mL (range 89.3-458.3). Conclusion: In contrast to the previously reported ML II patients, our data suggest that the residual activity of the GlcNAc-1-phosphotransferase in MLIII gamma is sufficient to allow the targeting of lysosomal enzymes required for maintenance of B-cell functions. Support FIPE/CnPq.

JULY 25, 2015

Scientific Program

10:55 a.m

JULY 25, 2015

Scientific Program

11:07 a.m



## MANNOSE 6-PHOSPHATE-INDEPENDENT TRANSPORT MECHANISMS TO LYOSOMES

SANDRA MARKMANN

University Medical Center Hamburg-Eppendorf, Germany

GlcNAc-1-phosphotransferase is a hexameric enzyme complex ( $\alpha_2\beta_2\gamma_2$ ) that catalyzes the first step in the synthesis of the mannose 6-phosphate (M6P) recognition marker on lysosomal acid hydrolases required for efficient transport to lysosomes. Mutations in GNPTAB gene encoding the  $\alpha$ - and  $\beta$ -subunits of the GlcNAc-1-phosphotransferase associated with loss in its catalytic activity lead to mucopolysaccharidosis II (MLII, I-cell disease) characterized by missorting of multiple lysosomal hydrolases and the lysosomal accumulation of non-degraded material. Despite the lack of M6P residues, selected lysosomal enzymes reach normal levels in lysosomes of various cell types suggesting the existence of M6P-independent transport routes.

SILAC-based comparative quantitative analysis of lysosomal fractions isolated from fibroblasts deficient for the GlcNAc-1-phosphotransferase (PT<sup>ki</sup>) revealed unchanged amounts of 20% of lysosomal enzymes, including cathepsin D and

B. Examination of fibroblasts from a new mouse line lacking both M6P and sortilin, a multiligand type-1 receptor which has been reported to be an alternative transport receptor in the targeting of several lysosomal hydrolases, revealed that sortilin does not act as cargo receptor for cathepsin D and cathepsin B. Using fibroblast lines deficient for endocytic lipoprotein receptors we could demonstrate that both LDL receptor and Lrp1 mediate the internalization of non-phosphorylated cathepsin D and cathepsin B. Furthermore, the presence of Lrp1 inhibitor increased the secretion of cathepsin D from PT<sup>ki</sup> cells. These findings establish Lrp1 and LDL receptors in M6P-independent secretion-recapture targeting mechanism for lysosomal enzymes and might represent potential candidates for alternative therapeutic strategies and improved enzyme replacement therapies in MLII and other lysosomal disorders.

JULY 25, 2015

Scientific Program

11:19 a.m

## CENTRAL NERVOUS SYSTEM-DIRECTED GENE THERAPY FOR MUCOPOLYSACCHARIDOSIS VII

KATHERINE PONDER

Washington University School of Medicine, St. Louis, Missouri

Mucopolysaccharidosis VII (MPS VII) is due to deficiency of  $\beta$ -glucuronidase (GUSB), and results in the accumulation of glycosaminoglycans throughout the body. Neurological manifestations include mental retardation, which is likely due to accumulation of GAGs in cells of the brain such as neurons and microglial cells, and to associated neuroinflammation. Although systemic gene therapy with IV injection of a retroviral vector can result in low GUSB activity and reduce lysosomal storage in the brain, the effect is incomplete and will probably not prevent all manifestations. Recently, AAV vectors have demonstrated a remarkable ability to transduce neurons of the brain after either IV or intrathecal (IT) injection, but data of their efficacy in a large animal model of LSD are not available. MPS VII dogs were injected IV at 3 days of age or IT via the cisterna magna at 3 weeks of age with AAV vectors serotyped with AAV9 or rh10 capsid proteins, or IT at 3 weeks of age with a lentiviral vector pseudotyped with the VSG-G envelope protein. All vectors expressed the canine GUSB cDNA, which reduces the chance of an immune response in this model with a missense mutation (R166H). IV injection of AAV vectors was relatively inefficient, with GUSB activity only ~1% of normal in homogenates of cerebral cortex at 6 months, and only partial reduction in evidence of lysosomal storage as assessed by GM3 and LIMP2 immunostain. IT injection of AAV vectors was very efficient, achieving ~100% of normal GUSB activity in cortex, transduction of neurons as deep as 2 mm into the cortex, and near-complete resolution of lysosomal storage and neuroinflammation in the cortex. CSF GUSB activity was 15 U/ml and 430 U/ml for IV and IT injection of AAV vectors, respectively (normal is 10 U/ml). IT injection of lentiviral vector resulted in ~20% of normal GUSB activity in homogenates of cortex and 772 U/ml

of GUSB activity in the CSF, but neurons were not transduced, and there was evidence of lysosomal storage in regions that were 1 mm or deeper. Indeed, the major cell type that appeared to be transduced was the endothelial cell. Although IT injection of AAV9 or rh10 vectors was quite effective at transducing neurons of the cortex, cerebellum, brainstem, and spinal cord, transduction of the caudate, thalamus, and midbrain was much less effective, and could be problematic for some disorders. Future studies will assess storage and neuroinflammation in these regions of the brain. It is likely that AAV vectors enter the cortex from the CSF via the Virchow-Robin space that surrounds blood vessels that enter the brain from the surface, and cross the pia mater to enter the parenchyma and transduce neurons. IT injection of AAV9 or rh10 appears to have a strong potential for treating brain in MPS VII and other LSD, and is much more efficient than IV injection, while AAV vectors given IT were superior to lentiviral vectors given IT. Expression has been maintained in CSF for up to 14 months with IV injection of AAV vectors. However, peripheral disease of the bones and joints was not effectively treated with an IT injection, and another approach will be needed to treat peripheral disease. These data with the lentiviral vector suggest that injection of enzyme into the CSF will not prevent all lysosomal storage, as very high CSF GUSB activity did not prevent lysosomal storage at 1 mm or deeper in the cortex. This study was done in collaboration with Mark Haskins of the University of Pennsylvania.

JULY 26, 2015

Scientific Program

8:30 a.m





### INTRACEREBROSPINAL FLUID AAV-MEDIATED GENE THERAPY FOR MPS III

FATIMA BOSCH

Center of Animal Biotechnology and Gene Therapy. Universitat Autònoma Barcelona. Bellaterra. Spain

Mucopolysaccharidosis Type III or Sanfilippo Syndrome comprises 4 autosomic recessive disorders caused by mutations in genes that encode for enzymes involved in the stepwise degradation of heparan sulphate (HS). Accumulation of HS in lysosomes leads to lysosomal pathology, and affected patients undergo severe neurodegeneration with mild somatic disease, and usually die during adolescence. Sanfilippo constitutes an unmet medical need. This presentation will discuss the potentiality of intracerebrospinal AAV-mediated gene therapy to counteract neurologic and somatic MPSIII. The results of this study provide strong evidence supporting the clinical translation of the approach.

JULY 26, 2015

Scientific Program

8:55 a.m

### HEMATOPOIETIC STEM CELL BASED GENE THERAPY FOR THE TREATMENT OF LYSOSOMAL STORAGE DISORDERS

ALESSANDRA BIFFI, M.D.

San Raffaele Scientific Institute, Milan, Italy

In most Lysosomal Storage Disorders (LSD) hematopoietic stem cell (HSC) transplantation is not or poorly effective. HSC gene therapy could ameliorate the outcome of allogeneic transplant and provide an expectation of efficacious treatment for these LSD. HSC can be genetically modified to express supra-normal levels of the therapeutic enzyme, and become a quantitatively more effective source of functional enzyme than normal donor's cells. Moreover, autologous HSC are immediately available, thus saving precious time in rapidly progressing forms, and can significantly reduce transplant-related morbidity and mortality. We are thus implementing an innovative approach based on the transplantation of autologous, gene corrected HSC for the treatment of severe LSD lacking efficacious and safe therapeutic opportunities. To this goal, we exploit the features of lentiviral vectors (LV). By using LV for HSC gene correction, we proved the therapeutic potential of HSC gene therapy in the murine model of three different LSDs. In the case of metachromatic leukodystrophy (MLD), a severe dysmyelinating LSD, preclinical research led to Phase I/II clinical testing. Indeed, a clinical trial of HSC gene therapy for MLD is currently on going. Evidence of tolerability

and safety of the proposed approach, as well as of therapeutic efficacy in the treated patients have been obtained. The same approach has been applied with success to the murine models of type I Mucopolysaccharidosis (MPS I), a LSD characterized by visceral organ, skeleton and nervous system involvement, and of globoid leukodystrophy (GLD), a demyelinating LSD similar to MLD. A clinical development plan for these two diseases has been started with a Phase I/II trial of HSC gene therapy for MPSI patients planned for late 2015. We are also experimentally addressing the critical need of enhancing brain microglia turnover with donor cells following HCT in order to anticipate the time of clinical benefit and improve the efficacy of the transplant procedure. This work thus far provided hints for designing novel and less invasive approaches for treating LSDs having a prevalent or exclusive CNS involvement.

JULY 26, 2015

Scientific Program

9:20 a.m



## A JOURNEY FROM MATURING RBC AND PLATELETS TO CROSSING THE BBB FOR TREATMENT OF CNS DEFICITS IN MPS I MICE

DAO PAN, M.S.,PH.D.

University of Cincinnati College of Medicine

The long-term therapeutic potential of hematopoietic stem cell (HSC)-mediated gene therapy has been demonstrated in several clinical trials of genetic diseases including LSDs, yet the paradox of the desire for high transgene frequency and associated increased risk of oncogenesis remains unresolved. Restricting transgene expression to maturing erythroid cells and platelets can reduce the risk of activating oncogenes in HSCs and all their progeny, yet take advantage of their robust protein-synthesis machinery, abundance and relatively quick turnover for effective protein production. Utilizing a mouse model of Mucopolysaccharidosis type I (MPS I), we sought to evaluate the feasibility and efficacy of reprogramming erythroid and megakaryocyte lineages for production, distribution and delivery of a lysosomal enzyme, alpha-L-iduronidase (IDUA). We have shown that maturing RBC and megakaryocytes are capable of producing large amounts of IDUA with proper catalytic function, lysosomal trafficking and receptor-mediated uptake, which could be sorted to and stored within RBC and platelets. The transgene-derived IDUA enzyme can be released directly into the extracellular space (into circulation) or within microparticles during reticulocyte formation, megakaryocyte maturation or platelet activation, and is capable to correct deficits in cells from MPS I patient. Sustained and supraphysiological levels of IDUA in the circulation were achieved in MPS I mice with only moderate transgene dosage (0.3 copy per HSC genome) when utilizing both lineages for IDUA

expression from a hybrid IHK promoter, leading to complete correction in all peripheral organs tested. Importantly, significant improvement (not a cure) of brain pathology and behavioral deficits were observed.

To facilitate IDUA protein across the blood-brain barrier (BBB), we investigated whether fusion of the receptor-binding domain of apolipoproteins with IDUA can bind to low-density lipoprotein receptors on the BBB and be transcytosed into the CNS. After in vitro screening and in vivo evaluation in MPS I mice, we identified a small potent peptide (e) that could empower a widespread delivery of IDUAe fusion protein into CNS. The long-term CNS biodistribution, dose-correlation, and therapeutic benefits of BBB-targeted IDUAe were further evaluated after long-term, peripheral delivery via HSCs-mediated gene therapy when restricting gene expression to erythroid/megakaryocyte lineages. Brain metabolic correction and normalization of exploratory-behavior deficits were observed in MPS I mice by long-term physiological levels of IDUAe derived from moderate HSC transduction efficiency (0.1 copy per cell), a performance superior to that by 15-fold higher levels of non-targeted IDUAc control protein. Importantly, these levels of IDUAe proved to be more beneficial for CNS treatment than wild-type HSCs fully engrafted in MPS I chimeras. Together, our proof-of concept experiments provide compelling evidence for CNS efficacy of IDUAe and its prospective translation to clinical application.

JULY 26, 2015

Scientific Program

10:05 a.m

## CHAPERONE-MEDIATED GENE THERAPY FOR TYPE I SIALIDOSIS

IDA ANNUNZIATA (ALESSANDRA D'AZZO LABORATORY), PH.D.

Department of Genetics, St. Jude Children's Research Hospital, Memphis TN 38105, USA

Sialidosis is a rare neurosomatic lysosomal storage disease (LSD) caused by deficiency of the lysosomal sialidase N-acetyl- $\alpha$ -neuraminidase-1 (NEU1). Patients are diagnosed with Type II dysmorphic or Type I normomorphic form of the disease, based on the age of onset and severity of their symptoms. Type II cases share many clinical signs with early infantile galactosialidosis, the LSD caused by combined deficiency of NEU1 and  $\beta$ -gal, due to a primary defect of the protective protein/cathepsin A (PPCA). Patients with type I sialidosis instead develop an attenuated, non-neuropathic form of the disease, also known as "cherry red spot myoclonus syndrome", with symptoms arising during juvenile/adult age. No cure is currently available for sialidosis. However, given the strict dependence of NEU1 on PPCA for its stability and activity in lysosomes, we have investigated the potential use of a PPCA-mediated therapy for the attenuated Type I form of sialidosis. This idea was spearheaded by the observation that NEU1 activity can be increased by titrating the levels of available PPCA.

We have generated a mouse model of Type I sialidosis by crossing Neu1 $-/-$  mice with a transgenic line expressing a Neu1 variant with a V54M amino acid substitution, identified in an adult Type I patient. Neu1 $-/-$ ;Neu1V54M mice are viable and fertile with no apparent early symptoms of disease, no neurological involvement and low residual Neu1 activity in all organs. Overt

signs of the disease appear at 1-2 years of age, and include edema, enlargement of the kidneys with vacuolization of the tubular epithelium, and oligosacchariduria. To complement the levels of endogenous PPCA in the Neu1 $-/-$ ;Neu1V54M mice we have used a self-complementary AAV vector, expressing PPCA under the control of a liver specific promoter (sCAAV2/8LP1-PPCA). This vector has been employed in a large preclinical study for the treatment of galactosialidosis. Neu1 $-/-$ ;NEU1V54M mice received a single dose injection of sCAAV2/8LP1-PPCA at 1-year of age and were euthanized 1 month later. High expression of the PPCA enzyme in the liver of the injected mice resulted in about 3 fold increase of the Neu1V54M basal activity in all tissues tested, improved tissue pathology and decreased levels of high molecular weight sialyl-oligosaccharides in the urine compared with not injected mice. Considering that the majority of NEU1 mutations so far identified do not involve the catalytic site of the enzyme, this pharmacologic, PPCA chaperone-mediated therapy may be effective for other NEU1 mutations found in patients with Type I sialidosis.

{This work was funded in part by NIH grants GM60905 and DK52025, the Assisi Foundation of Memphis, the American Lebanese Syrian Associated Charities (ALSAC) and the National Tay-Sachs & Allied Disease Association (NTSAD).}

JULY 26, 2015

Scientific Program

10:30 a.m



## PHARMACOLOGICAL CHAPERONING IN FABRY AND SCHINDLER DISEASES

SCOTT C. GARMAN AND MATTHEW C. METCALF

Department of Biochemistry & Molecular Biology, University of Massachusetts Amherst, Amherst MA 01003

Lysosomes contain a large number of enzymes responsible for the catabolism of macromolecules. In humans, the two homologous enzymes  $\alpha$ -galactosidase ( $\alpha$ -GAL) and  $\alpha$ -N-acetylgalactosaminidase ( $\alpha$ -NAGAL) are deficient in the lysosomal storage diseases known as Fabry and Schindler diseases, respectively. One approach under clinical investigation for the treatment of the lysosomal storage diseases uses a small molecule to stabilize the folded form of the protein. Using X-ray crystallography, we have determined the three-dimensional structures of the human  $\alpha$ -GAL and

$\alpha$ -NAGAL enzymes, both alone and in complex with a range of potential pharmacological chaperones. The structural and biochemical studies reveal the molecular basis for pharmacological chaperoning in the family of enzymes. Using rational ligand design, we were able to engineer affinity improvements of greater than 9 kcal/mol (i.e. 1 million fold tighter binding) in small molecules that stabilize the enzymes. We will present guidelines for improving the specificity and affinity of compounds for these and other lysosomal enzymes.

JULY 26, 2015

Scientific Program

10:55 a.m

## CHOROID PLEXUS-DIRECTED VIRAL GENE THERAPY FOR ALPHA-MANNOSIDOSIS, A PROTOTYPICAL LYSOSOMAL STORAGE DISEASE

EUN-YOUNG CHOI

National Institute of Child Health and Human Development, Bethesda, MD

The choroid plexuses are vascularized structures that project into the cerebrospinal fluid (CSF). The specialized polarized epithelia of choroid plexuses produce CSF by transporting water and ions into the ventricles, and are post-mitotic, i.e., do not undergo turnover. We hypothesized that remodeling these epithelia to secrete missing lysosomal enzymes by one-time CSF administration of a recombinant AAV (rAAV) could be an attractive strategy for long-term treatment of lysosomal storage diseases (LSDs). Lysosomes function as digestive units of cells and specific enzymes within lysosomes break down nutrients. Patients with LSDs cannot metabolize certain nutrients, resulting in diminished lifespans and reduced quality of life. CSF-directed recombinant enzyme replacement has shown promise for several LSDs but requires repeated instillations due to short recombinant enzyme half-lives. In contrast, rAAV-mediated gene transfer to the choroid plexus could enable continuous synthesis of lysosomal enzymes and steady delivery to the brain globally.

To evaluate this hypothesis, we obtained an alpha-mannosidosis mouse model generated by targeted disruption of the lysosomal acid-mannosidase (LAMAN). We cloned the human (hu) LAMAN cDNA into a rAAV shuttle plasmid and generated high titer rAAV5 expressing huLAMAN. We administered viral particles to the CSF of homozygous mutant mice by brain lateral ventricle injection on day 3 of life. We documented dose-dependent transduction and huLAMAN mRNA expression confined to the choroid plexuses of rAAV5-treated animals. Brain biochemical analyses at 1, 2 and 6 months post-treatment documented sustained increases of LAMAN enzyme activity globally across the brain. By 8 months of age, untreated mutant mice showed prominent lysosomal vacuoles in hippocampal neurons, in contrast to rAAV5-LAMAN treated mutants for which brain histopathology was comparable to wild-type. If choroid plexus-targeted viral gene therapy approach were similarly successful in larger animals and human subjects, the most significant current barriers to health for patients with LSDs could be circumvented.

JULY 26, 2015

Scientific Program

11:20 a.m





## IDENTIFICATION OF THE AMINO ACIDS INSERTED DURING NONSENSE SUPPRESSION AND THEIR FUNCTIONAL CONSEQUENCES IN A CYSTIC FIBROSIS MODEL

DAVID BEDWELL  
University of Alabama

Premature termination codons (PTCs) account for ~11% of all mutations that cause human genetic diseases. PTC suppression (nonsense suppression) is a strategy aimed at bypassing a disease-causing PTC so that synthesis of the full-length protein is restored. If the amino acid inserted at the PTC is the wild type or another compatible with protein function, a phenotypic improvement should be possible. Currently, the identity of the amino acids inserted during PTC suppression in mammalian cells remains unclear.

PTCs occur in ~10% of cystic fibrosis (CF) patients, and the CFTR-G542X mutation is the most common PTC allele. We found that suppression of a UGA codon in the CFTR-G542X context resulted in the insertion of three amino acids: arginine, cysteine and tryptophan. Insertion of these amino acids occurred by near-cognate

mispairing of an aminoacyl-tRNA with mismatches at either the first or third positions of the codon-anticodon interaction. Analysis of each of these changes individually revealed that each missense construct restores only a fraction of the cAMP-stimulated chloride channel activity of wild type CFTR. Notably, each also exhibited partial defects in protein maturation from band B (the ER form of CFTR) to band C (the mature form). We found that both CFTR correctors and potentiators enhanced CFTR activity from these constructs to varying extents. Our results suggest that CFTR activity restored by PTC suppression can be enhanced significantly when combined with other pharmacological agents. This therapeutic approach should also be amenable to other genetic diseases caused by PTCs, including the glycoproteinoses.

JULY 26, 2015

Scientific Program

11:32 a.m

## WHERE WE HAVE BEEN, WHERE WE ARE, AND WHERE ARE WE GOING? - INCLUDING LARGE ANIMAL MODELS

MARK HASKINS, VMD PH.D.

Washington University School of Medicine, St. Louis, Missouri

The discussion will include definitions and some of the history of the study of genetic diseases (Newton, Garrod) and lysosomal storage diseases (de Duve, Neufeld, Sly), clinical descriptions (from alpha-mannosidosis in 1967 to Shindler Disease 20 years later), discoveries leading to understanding the functional abnormalities (the pathogenesis), and current approaches to therapy including:

- Symptomatic – physical therapy, growth hormone, corneal transplantation, joint replacements, feeding tubes
- Enzyme Replacement Therapy including the first “experiment of nature” for alpha-mannosidosis – IV and intrathecal – the blood brain barrier - high dose therapy; enzyme without mannose 6-phosphate; receptor tagged (i.e. transferrin)

- Substrate Reduction Therapy – small molecules to decrease substrate biosynthesis
- Chaperones – to stabilize mutant protein
- Stop codon read-through
- Transplantation – bone marrow, cord blood, chondrocytes, mesenchymal stem cells
- Modify the lysosomal network; upregulate autophagy
- Anti-inflammatory therapy – inhibit inflammatory molecules: cathepsins, MMPs, TNF-alpha
- Gene therapy – systemic and for the central nervous system and the characteristics and usage of current large animal models

JULY 24, 2015

Family Program

10:35 a.m



## CURRENT AND FUTURE THERAPIES

MARC PATTERSON, M.D., FRACP, FAAN, FANA  
Mayo Clinic Children's Center, Rochester, MN 55905 USA.

Although there are few disease-modifying therapies available for glycoprotein storage disorders, all people affected by these disorders can be treated. Impeccable general pediatric or medical care, coupled with a balanced diet and exercise tailored to the individual's abilities make a significant difference to quality and quantity of life. The effectiveness of such an approach has been demonstrated in a common genetic disorder for which, until recently, there was no definitive therapy – cystic fibrosis. The lifespan for cystic fibrosis has increased several-fold in the last fifty years, reflecting the development of expert centers that provide multidisciplinary care, and the parallel refinement of evidence-based guidelines defining best practices in clinical care. Improvements in nutritional support (particularly in gastrostomy technology and respiratory therapies) have improved outcomes in lysosomal diseases, and these gains can be further enhanced by building networks of expert centers and implementing standards of care.

There are several potential approaches to disease-modifying therapies for glycoprotein storage diseases, all of which result from genetically determined derangements of lysosomal biology. The most logical approach would be to correct the underlying mutations (easily achievable in bacteria, not so in humans); the next, to replace the defective gene with intact copies by gene transfer. Gene transfer has been refined in animal models, has become routine in research laboratories, but major hurdles remain before gene transfer can

be effectively implemented in human disease that involves the nervous system and other highly structured organs. A more recent technique involves the use of micro RNAs to enhance or inhibit the expression of genes of interest, which could be used to target the primary pathogenic gene, or genes in alternate pathways that might ameliorate the expression of disease. Moving further along the pathway, enzyme replacement therapy has proven effective in several lysosomal diseases, particularly in correcting the function of the bone marrow, liver and spleen, but is less effective in the skeleton, and minimally effective, if at all, in the nervous system. It is also expensive and requires frequent intravenous (and, in some cases, intrathecal) infusions. An alternative to replacement of the defective protein (enzyme) is to enhance the function of the protein that is present, by means of small molecules known as chaperones, which can allow misfolded mutant proteins to evade the cell's quality control system and reach their site of action in the lysosome. Chaperon (or enzyme enhancement) therapy is being studied in several lysosomal diseases at present.

In the United States, the federal government has recognized the importance of rare diseases by establishing special programs to encourage the development of specific treatments – most notably the TRND (Therapies for rare and neglected diseases) program, which provides substantial support for the preclinical development and early clinical trials of drugs for these diseases. Other countries are also developing similar programs.

JULY 24, 2015

Family Program

11:00 a.m

## RARE TRAIT RESEARCH GROUP FOR ASPARTYLGLUCOSAMINURIA

JULIA TARAVELLA

Our first child, Daniel was born in 1994 as a beautiful, perfect, and healthy baby. When he was three years old, we accepted that he was somewhat behind other kids. We had a great support at school, community and private therapists. Daniel worked very hard to become a normal kid despite his diagnosis of autism spectrum disorder (PDD-NOS). We started noticing the same problems with Alexander when he was a little over one year old. From that moment on, we knew that our boys did not have just allergies, infections, low muscle tone, diarrhea, short attention span, etc. It was something else that was taking our kids life away from them, and taking them from us. I started the search for the answers!

It took us 16 years to learn our children's correct diagnosis. When we finally learned the correct diagnosis in 2012, it devastated us. Both of our children have Aspartylglucosaminuria (AGU), a rare fatal disease. During the years we spent looking for an answer, we never had a doubt that when we found it, we could cure our boys and give them a

chance for a normal life. Unfortunately, when finally we knew the problem, we could not help them. Being told that one's child is going to suffer and die prematurely is the most tragic and bottomless experience in life. But it can be worse. During several months after diagnoses, we found out that not only there is no treatment for the disease, no one is looking for a cure.

Equipped with the knowledge of the problem and no place to go, we decided to work on a solution and save kids' lives. This is when our real journey began!

We interviewed many researchers and discussed the ideas about the development of AGU treatment. In December of 2012, we started a project with University of North Carolina to develop a treatment for AGU and to help our kids and all AGU patients around the world. In 2013, we started to support AGU research work in Germany. Support for the research comes from ongoing fundraising activities.

JULY 24, 2015

Family Program

11:25 a.m



## FACTS AND HYPOTHESES, OLD AND NEW, ON ML II AND ML III, PRIMORDIALLY DISORDERS OF CONNECTIVE TISSUE

JULES LEROY, M.D.,PH.D. AND SARA CATHEY, M.D.

**Emeritus Professor and Chairman of the Departments of Paediatrics and Medical Genetics, Ghent University Hospital and Medical School, Ghent, Belgium.**

Thomas (1973) pointed to a common pathogenesis and causation. Spranger (1970) already had listed both among the mucopolysaccharidoses, based mainly on shared radiographic features. During this era of elucidation of the single primordial enzyme defect in many inborn errors of metabolism, the deficiency of many acid hydrolases in "I-Cells" was observed in addition to their hyperactivity in surrounding culture media and in the patients' body fluids; either phenomenon was more severe in ML II than in ML III cells. Apparently the acid hydrolases did not reach their normal lysosomal destination in the cells and hence were lost into the culture media or the extracellular matrix. All of them were shown to lack a common key factor apparently needed to enter lysosomes. Work by Neufeld and by Sly and their research groups identified and characterized this biochemical key as the mannose-6-phosphate (M6P) recognition marker, present in lysosomal enzymes of normal people. The marker is especially important in soft connective tissue and cartilage cells. In 1980 the lab of S. Kornfeld here in St. Louis was one of two that independently elucidated the common primordial enzyme defect in ML II and ML III: the failing of GlcNac-phosphotransferase (GNPT), the catalyst of the first step in the M6P marker synthesis. This important result was the stepstone for characterization of the enzyme complex and of identifying GNPTAB and GNPTG as the genes encoding its polypeptide components. There is nearly no residual GNPT activity in ML II

and less than 10% of its normal activity in ML III patients. This residual activity explains that the latter type of patient is recognized clinically only from early or later childhood. The disease shows more gradual growth failure, milder "dysostosis multiplex" and normal intelligence or only mild intellectual disability. ML III patients have a better life expectancy. However from later adolescence joint stiffening and especially painful hip disease significantly reduce quality of life. It is obvious that in either disease bone quality is not normal and certainly not adequately maintained. Radiographs in infantile ML II patients prove that bone is not built normally. The hard connective tissue features in ML are reasonably well studied, but their morbidity insufficiently understood. Nearly no attention has been paid to studying the soft connective tissues, major components in and about joints, ligaments and tendons. Even more importantly soft connective tissue forms the major structure in the cardiac valves and in bronchial and pulmonary tissues. The latter two are frequently involved in the ultimate fatal outcome of either disease. These extracellular matrix tissues with initial quality already below the norm, show progressive hardening and dysfunction. Much more biochemical and molecular biology work, mainly regarding disturbed balances of extracellular signaling, is required before our ambition to find an effective treatment can come nearer fulfillment.

**JULY 24, 2015**

Family Program

1:15 p.m

## SURGICAL MANAGEMENT OF CERVICAL, THORACIC AND LUMBER SPINE

MICHAEL KELLY

*Abstract will be given out on the day*

**JULY 24, 2015**

Family Program

1:35 p.m





## MANAGEMENT OF UPPER LIMB ISSUES IN MUCOLIPIDOSIS

RICHARD MORBEY

Consultant Surgeon – Tauranga Hospital, New Zealand

Mucopolidosis III is a rare congenital disorder which has profound effects on the Musculo-skeletal system. Not only does it produce a severe osteodystrophy affecting both bones and joints but the deposition of abnormal material in the soft tissues also affects tendons, ligaments and nerves. As a consequence it has major impact on limb function and mobility.

This paper discusses my experience in managing the upper limb problems in 2 patients from one family affected with Mucopolidosis III.

While a number of the problems encountered can be managed with standard Orthopaedic treatment, the unique nature of the disorder and the way it affects the tissues requires an alternative approach in certain situations.

JULY 24, 2015

Family Program

1:55 p.m

## CARDIAC ISSUES - WHAT ARE THE ISSUES / WHAT TO DO

NICK PIETRIS

University of Maryland School of Medicine

There is limited data describing the cardiac manifestations found within the glycoproteinoses. Detailed descriptions of the cardiac findings in this group of patients are limited. Glycoproteinoses clinics were held at the Greenwood Genetic Center. The findings of echocardiography were previously presented (Pietris et al. (2013). Echocardiographic findings in patients

diagnosed with glycoproteinoses diseases. *Molecular Genetics and Metabolism*, 108, S75. doi:10.1016/j.ymgme.2012.11.197 ). In addition to echocardiography, detailed clinical histories and electrocardiograms were obtained. The findings of this study will be reviewed in addition to clinical considerations of patient management.

JULY 24, 2015

Family Program

3:25 p.m



## SCHOOLING ISSUES / SPECIAL EDUCATION / IEPs

LUCIA HOROWITZ, PH.D.  
Greenwood Genetic Center, SC

What do you need to know to be your child's best educational advocate? This presentation will include a discussion of how to decide which skills your child needs to learn, what kind of help and environmental supports your child may need to make effective learning happen, and ways to support your child to help maximize functional learning. A list of resources for parents will be included.

**JULY 24, 2015**

Family Program

3:50 p.m

**JULY 25, 2015**

Family Program

10:55 a.m

## OVERVIEW NEUROLOGICAL IMPLICATIONS

MARC PATTERSON, M.D., FRACP, FAAN, FANA  
Mayo Clinic Children's Center, Rochester, MN 55905 USA.

The most frequent neurologic manifestation of glycoprotein disorders is cognitive impairment. Global impairment of cognitive abilities that impairs function is designated "intellectual disability" in the United States; different terms are used elsewhere, such as "learning disorder" in the United Kingdom. Because cognition engages multiple brain regions and networks, intellectual disability is not localizable, as is the case with classic neurologic syndromes. Brain imaging techniques, such as conventional MRI, may show no abnormalities in patients with profound intellectual impairment, whereas other patients may show white matter and other variations, without minimal, if any, effect on cognition. In early childhood, before intelligence can be adequately assessed, most individuals destined to have intellectual disability will be diagnosed with developmental delay – sometimes restricted to speech and language, but more often global (involving two or more of the traditional developmental domains, of language, social adaptation, and gross and fine motor skills). Intellectual disability implies a static process, in which cognitive ability has reached a plateau, but does not decline further, in contrast to dementia, which is characterized by progressive loss of intellectual abilities across all domains, although it may be first manifest as memory loss, impaired language or behavior. Both intellectual disability

and dementia may occur in glycoprotein storage disorders. Differentiating the two may be very difficult in children. Establishing an accurate diagnosis is essential to school and employment planning.

The cerebellum is frequently affected in glycoprotein and other lysosomal disorders. The Purkinje cells, through which all of the output of the cerebellum passes, are large metabolically active cells. Their dysfunction leads to familiar signs and symptoms – unsteady gait (ataxia), impaired coordination, tremor, and incoordinated swallowing (dysphagia) and irregular articulation (dysarthria). Imaging usually shows disproportionate atrophy of the cerebellum compared to the cerebral hemispheres, and microscopic examination of the tissues shows characteristic inclusions in cells, with evidence of storage.

Variable involvement of other levels of the nervous system occurs in glycoprotein disorders, including basal ganglia dysfunction (manifest as movement disorders), myelopathy (spinal cord disease) causing spastic gait and peripheral neuropathy, causing loss of reflexes weakness and sensory impairment. Symptomatic management is available for all of these manifestations of nervous system dysfunction.

**JULY 25, 2015**

Family Program

8:30 a.m



## FUCOSIDOSIS - PRESENT KNOWLEDGE AND FUTURE PROSPECTS

MICHAEL BECK, M.D.

Institute of Human Genetics University of Mainz, Germany

Fucosidosis is an autosomal recessive storage disorder caused by the defect of the enzyme alpha-fucosidase. The FUCA1 gene, that codes for  $\alpha$ -fucosidase, is located on chromosome 1. Clinically, fucosidosis is characterized by neurodegeneration with progressive mental and motor deterioration. Further clinical signs include dysmorphic face, gingival hypertrophy, angiokeratoma, enlarged liver and spleen, eye abnormalities and hearing loss. MRI examination of the CNS reveals a generalized hypomyelination of white matter tracks. In the past, two phenotypes had been distinguished: A severe infantile form, designated type I, and a milder form, referred to as type II. But this classification seems to be arbitrary, as studies of a large number of patients have shown that type I and II rather represent the extremes of a continuous clinical spectrum.

Nowadays, besides palliative care for the treatment or alleviation of symptoms, bone marrow transplantation is the only therapeutic option for patients affected by fucosidosis. The benefit of this procedure, however, is limited by the fact that the disease progression is very fast and cellular and tissue damage cannot be rescued by the transplanted cells. There exist animal models of fucosidosis that allow the evaluation of new therapeutic interventions. An ex-vivo gene therapy experiment was performed in a canine model whereby a retroviral gene transfer into autologous hematopoietic stem cells was used. But this procedure was unsuccessful, as graft failure occurred in all transplants.<sup>1</sup>

In order to overcome the blood-brain barrier, recombinant fucosidase was applied intracisternally to young affected dogs. After three monthly injections an increase of enzyme activity and a decrease of oligosaccharide storage could be demonstrated in all brain areas.<sup>2</sup> Although this

JULY 25, 2015

Family Program

9:15 a.m

procedure was safe and well-tolerated, it remains questionable whether it can ever be used also in humans.

An analysis of the fucosidase gene revealed 22 different gene alterations, including 4 missense mutations and 18 nonsense mutations, that consisted of 7 stop-codon mutations and 11 other complex changes.<sup>3</sup> Stop-codon mutations lead to premature translation termination and to the synthesis of a non-functional enzyme. It is known that the drug gentamicin is able to induce the so-called "read-through" of premature stop-codons and to restore production of full-length proteins with normal enzymatic activity.<sup>4</sup> This therapeutic principle has been applied in cell culture systems, in an animal model of mucopolysaccharidosis type I and in a clinical trial in Duchenne muscular dystrophy patients, whereby newly designed drugs were used that are less toxic than gentamicin. The "read-through" method seems to be a promising therapeutic approach, but of course is suitable only for patients who carry a stop-codon mutation.

As it has often been shown that early treatment is necessary to prevent irreversible organ damage, newborn screening has been or will be established in many countries. In the future it can be expected that more effective therapies, for example gene therapy, personalized medicine such as read-through drugs, and early initiation of treatment may change the prospect for fucosidase patients.

### Literature

1. Ferrara ML, Occhiodoro T, Fuller M, et al. Canine fucosidosis: a model for retroviral gene transfer into haematopoietic stem cells. *Neuromuscul Disord.* 1997;7:361-366.
2. Kondagari GS, King BM, Thomson PC, et al. Treatment of canine fucosidosis by intracisternal enzyme infusion. *Exp Neurol.* 2011;230:218-226.
3. Willems PJ, Seo HC, Coucke P, et al. Spectrum of mutations in fucosidosis. *Eur J Hum Genet.* 1999;7:60-67.
4. Keeling KM, Xue X, Gunn G, et al. Therapeutics based on stop codon readthrough. *Annu Rev Genomics Hum Genet.* 2014;15:371-394.

## HEMATOPOIETIC CELL TRANSPLANT FOR GLYCOPROTEINOSSES

TROY C. LUND, MSMS M.D., PH.D. FAAP

University of 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 mucopolysaccharidoses (ML II and III), and sialidosis. The defect 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 cell transplant (HCT) with either bone marrow or umbilical cord blood as cell sources has been used as a therapeutic treatment. The rationale 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 HCT is used to cross-correct a lysosomal defect and achieve a neuronal-sparing result (as well as life extending).

Similarly, HCT has been performed in the setting of glycoprotein lysosomal storage diseases with mixed results depending on the disease. Dr. Lund will discuss what is known about HCT 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 from: no change in disease and clinical status to possible disease stabilization such as in the use of HCT in alpha-mannosidosis; there may even be improvement in some disease manifestations: i.e. cognitive function, gait, and hearing. On the contrary, HCT for ML-II (I-cell disease) disease has not been published extensively, but 23 patients around the world have received HCT for ML-II (current study data). HCT for ML-II most likely does not alter disease course based on our analyses of the first comprehensive study of HCT outcomes for I-cell disease. Whether HCT for any glycoprotein disorder can be augmented by gene therapy techniques, recombinant enzyme, or through the use of primordial stem cells (embryonic) is not known, but may hold promise in the future.

JULY 2, 2015

Family Program

10:05 a.m





## NEW HORIZONS IN THE DEVELOPMENT OF THERAPIES FOR GLYCOPROTEINOSSES

ALESSANDRA D'AZZO\*, PH.D. AND JENNY NOBLE

\*Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN, USA

The glycoproteinoses comprise a group of lysosomal storage diseases (LSDs), whose common hallmark is the genetic defect of a lysosomal protein involved in the catabolism of glycoproteins. The deficient proteins may be a glycosidase, a protease, a lysosomal membrane carrier, or a synthetic enzyme. Elevated urinary excretion of oligosaccharides is diagnostic of these diseases. As in other LSDs, the glycoproteinoses present clinically with a spectrum of disease severity that mostly correlates with the extent to which the defective protein maintains its function(s). Individually, the glycoproteinoses are considered rare diseases for which no therapy is currently available. However, some of the attenuated forms are often misdiagnosed or mistaken for other clinical conditions, hence their incidence in the population may be underestimated. Natural or genetic engineered animal models of all the glycoproteinoses are available. These models have been exploited for investigating mechanisms of pathogenesis and for experimenting different therapeutic approaches. Overall these studies have moved the field forward in unforeseen directions, because they have uncovered functions of lysosomal proteins in basic cellular pathways that are affected not only in these pediatric diseases but also in more common adult disorders associated with aging. These interesting findings have sparked the interest of biotech companies, willing to invest effort in the development of therapies for glycoproteinoses that may eventually be applicable to a broader population of patients. To date, enzyme replacement therapy (ERT) is the

most exploited approach for treatment of LSDs, but ERT is not widely applicable because it depends on the nature and chemical properties of the deficient enzyme. Thus, scientists and clinicians have experimented with substrate reduction therapy (SRT), currently used in the clinic for some LSDs, chaperone-mediated therapy and gene therapy, all of which have been tested in animal models with variable success. For the glycoproteinoses there are currently three clinical trials in the pipeline; ERT has been already tested in a small cohort of patients with alpha- mannosidosis, and both ERT and AAV-mediated gene therapy are being developed for the treatment of galactosialidosis and potentially sialidosis type I. Given the renewed attention to treat orphan diseases, and the potential use of novel therapeutic approaches that can be tailored to the characteristics of individual diseases, we strongly believe that the time is right for the development of therapies for the glycoproteinoses. However, success in this endeavor will depend on the cooperative and coordinated effort of expert clinicians, basic scientists, pharmaceutical companies and patients advocacy group.

## Speaker Profiles



Member and Endowed Chair

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### ALESSANDRA D'AZZO, PH.D.

Alessandra d'Azzo graduated in Biology and received a doctorate in Genetics from the University of Milano, Italy; and a Ph.D. (cum laude) in Medical Cell Biology and Genetics from the Erasmus University, Rotterdam, The Netherlands. After a period at the National Institutes of Health as a Fogarty fellow, she went back to the Erasmus University and was appointed Assistant and then Associate Professor. She joined the St. Jude Faculty in Memphis USA in the early nineties and is currently a Full Member of the Genetics Department and an Adjunct Professor in the Dept. of Anatomy and Neurobiology at the University of Tennessee Health Sciences Center. She holds an Endowed Chair in Genetics and Gene Therapy.

The main focus of the research in d'Azzo's lab is on lysosomal biogenesis and lysosomal storage diseases (LSD); in particular, she studies the glycoproteinoses, sialidosis and galactosialidosis, and the glycosphingolipidosis, GM1-gangliosidosis, using faithful animal models of these LSD. She is also interested in muscle development and differentiation because of the discovery by her group of a muscle specific ubiquitin ligase involved in the maintenance of muscle homeostasis. Among those Sandra's considers the accomplishments of her research are: i) the discovery of the primary defect in galactosialidosis; ii) the identification of basic cellular pathways that are regulated by lysosomal enzymes and their substrates and that contribute to disease pathogenesis; iii) the development of enzyme replacement therapy and gene therapy for galactosialidosis. A gene therapy clinical trial for late onset galactosialidosis patients is scheduled to open in 2016. Through her seminal studies of the molecular mechanisms of disease pathogenesis in these pediatric LSD she has uncovered unexpected new functions of lysosomal enzymes and their substrates in more common adult neurodegenerative diseases, like Alzheimer's disease, that could have important implications in the biology and treatment of these conditions.

JULY 25, 2015

Family Program

10:30 a.m



### AMYRUTH BARTLETT, M.A., L.P.C.

AmyRuth Bartlett is a Nationally Certified Licensed Professional Counselor. Her Masters in Counseling is from Covenant Theological Seminary, and she holds a Bachelors degree in Psychology and Asian Studies from St. Olaf College.

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### ANA MARIA CUERVO, M.D., PH.D.

Dr. Ana Maria Cuervo is the Robert and Renee Belfer Chair for the Study of Neurodegenerative Diseases, Professor in the Departments of Developmental and Molecular Biology and of Medicine of the Albert Einstein College of Medicine and co-director of the Einstein Institute for Aging Studies. She obtained her M.D. degree and a Ph.D. in Biochemistry and Molecular biology from the University of Valencia (Spain) in 1990 and 1994, respectively, and received postdoctoral training at Tufts University, Boston. In 2002, she started her laboratory at the Albert Einstein College of Medicine, where she continues her studies in the role of protein-degradation in neurodegenerative diseases and aging.

Dr. Cuervo's group is interested in understanding how altered proteins can be eliminated from the cells through the lysosomal system (autophagy) and how malfunction of autophagy in aging is linked to neurodegenerative diseases.

Dr. Cuervo has been the recipient of prestigious awards such as the P. Benson Award in Cell Biology, the Keith Porter Fellow in Cell Biology, the Nathan Shock Memorial Lecture Award, the Vincent Cristofalo Rising Start in Aging Award, the Bennett J. Cohen award in basic aging biology and the Marshall Horwitz Prize for excellence in research. She also delivered the Robert R. Konh Memorial Lecture, the NIH Director's Lecture, the Roy Walford Endowed Lecture, the Feodor Lynen Lecture, the Margaret Pittman Lecture, the IUBMB Award Lecture, the David H. Murdoxk Lecture and the Gerry Aurbach Plenary Lecture. She is currently co-Editor-in-Chief of Aging Cell and associate editor of Autophagy. She has also received twice the LaDonne Schulman Teaching Award. Dr. Cuervo is currently member of the NIA Scientific Council and of the NIH Council of Councils.

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### ALESSANDRA BIFFI, M.D.

Alessandra Biffi, M.D., Pediatrician and Clinical Pharmacologist. She works as Head of Unit ("Hematopoietic stem cell gene therapy for lysosomal storage disorders") at the San Raffaele Telethon Institute for Gene Therapy and within the Pediatric Immunohematology and Bone Marrow Transplantation Unit of the San Raffaele Scientific Institute in Milano, Italy. Her research activity is directed towards the development and optimization of gene and cell therapy approaches for inherited pediatric disorders, with particular interest in lysosomal storage diseases, and her clinical activity dedicated to the extensive knowledge of the diseases of interest, in order to better address and direct therapeutic approaches, and to the experimental testing of the newly developed therapeutics in patients.



### BABAK RAZANI, M.D., PH.D.

Dr. Razani received his M.D., Ph.D. degrees from Albert Einstein College of Medicine. He conducted his clinical residency in Internal Medicine and clinical fellowship in Cardiology at Washington University School of Medicine/Barnes-Jewish Hospital followed by a Postdoctoral Research Fellowship in the area of cardiovascular metabolism with an emphasis on mechanisms of atherosclerosis.

He is currently Assistant Professor of Medicine and Pathology/Immunology at Washington University splitting his time as a cardiologist and running a research laboratory focused on the roles of the autophagy-lysosomal system in metabolic diseases such as atherosclerosis, obesity, and diabetes.

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### DAG MALM, M.D., PH.D.

Dr. med. Dag Malm graduated from the University of Göttingen, Germany, in 1978.

He has been:

- Assistant Professor at the Institute of Clinical Medicine, University of Tromsø, Norway (UiT) 1986 till 2010
- Chief Physician at the Gastroenterological section, Dep. Medicine, UNN, and as Section leader 1991 through 1996.
- Leader Norwegian Speciality Committee for Digestive Diseases 1998- 2014.
- Member Scientific Advisory Board in "The International Society of Mannosidosis" 1998- Still
- Member Union of Medical Specialists- European Board of Gastroenterology 2006- 2012 as the Deputy in the Training Recognition Committee of UMSG.
- In 2008 he started the clinic Tromsø Centre of Internal Medicine which he leads.

He became a specialist in Internal Medicine in 1985, in Gastroenterohepatology in 1990 and obtained a PhD degree in 1995. His doctoral thesis under Prof. Jon Florholmen was on the study of the regulation of insulin secretion in pancreatic islets, focusing on intracellular signal transduction in beta-cells with special reference to the effect of cholecystokinin, somatostatin, and galanin on the hydrolysis of phosphatidyl inositol.

In 1991, as a clinician, he initiated the "Tromsø Mannosidosis Group" together with the geneticist Øivind Nilssen and the biochemist Ole Kristian Tollersrud. The Group have purified Alpha-Mannosidase from a number of species, and were first to find the AA sequence and the human gene. Based on this, more than 150 disease-causing mutations have been detected, and a Database merging clinical, genetic and biochemical data was published on the web.

Together with 9 other European Research Groups, the University of Tromsø joined three European Union Projects (EURA-MAN, HUE-MAN, and ALPHA-MAN) with the purpose to characterize the disease at every level, and developing large scale production of Alpha-Mannosidase for Enzyme Replacement Treatment (ERT).

After numerous studies on Knock-out mice, the first human were treated in 2013.

Being a clinician, he has mainly been interested in patient groups, and in 1992 together with Paul Murphy, he created the first Homepage for Alpha-Mannosidosis in Tromsø and focused his research the design of clinical trials, understanding immune deficiency, characterizing psychiatric disease and developing non-invasive methods of detecting deposits in the brain.



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### DAO PAN, M.S., PH.D.

The research in Pan lab has focused on combining translational and basic research for virus-mediated (in vivo and ex vivo) gene transfer into stem cells, protein engineering, and their potential application toward treatment for patients with lysosomal storage diseases, with particular interests of ameliorating the central nervous system abnormalities and bone diseases in mucopolysaccharidoses and Gaucher Disease. Her efforts have centered in identifying new depot cells/blood lineages for in vivo long-term delivery of lysosomal enzymes, establishing in situ gene transfer into adult stem cells, and developing receptor-targeted delivery of lysosomal protein across the blood-brain barrier.

Dr. Pan is a tenured associate professor of pediatrics with primary appointment in the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's Hospital Medical Center, and a secondary appointment at the University of Cincinnati College of Medicine. Dr. Pan completed her B.S.-M.S. studies in Molecular and Cell Biology at Peking Normal University in Beijing, China. She was introduced into the fields of lysosomal storage diseases in Dr. Chet Whitley's lab, and was graduated with a Ph. D. in Molecular, Cellular, and Developmental Biology & Genetics from University of Minnesota in 1997. She continued to become a research associate in Pediatrics Department at University of Minnesota and later served as director of QPCR Core Facility. Her academic career has taken her from Research Assistant Professor in 2003 to her current position at Cincinnati Children's Medical Center. Dr. Pan has published over 40 research articles, and served on Gene & Cell Therapy of Genetic and Metabolic Diseases Committee for the American Society of Gene and Cell Therapy and an ADHOC member for several NIH Grant Review panels.





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### FATIMA BOSCH

Fatima Bosch is a Pharmacist (1980) and PhD in Biochemistry (1985) by the University of Barcelona. She conducted post-doctoral studies at Vanderbilt University (1985), Case Western Reserve University (1988-1990), and NCI/Frederick Cancer Research and Development Center (1991). She is currently Full Professor of Biochemistry and Molecular Biology (1999) and Director of the Center of Animal Biotechnology and Gene Therapy (2003) at the Universitat Autònoma Barcelona. She has been granted the Rey Juan Carlos I (1985), Francisco Grande Covián (1998), Narcís Monturiol (2002), Sant Jordi Cross (2005), Alberto Sols (2006) and ICREA Academia (2013) awards. She has been Founding member of the European Society of Gene and Cell Therapy (1992), President of the Spanish Society of Gene and Cell Therapy (2007-2009), Vice-President of the European Association for the Study of Diabetes (2009-2012) and member of the Gene Doping Expert Group of the World Anti-Doping Agency (2014-present).

Her research focuses on studying the pathophysiological causes of diabetes mellitus using transgenic animal models and developing gene therapy approaches to this disease by *in vivo* genetic manipulation of tissues using nonviral and viral vectors. Recently, she has applied her know-how on gene transfer technologies to the development of gene therapies for inherited metabolic disorders such as Mucopolysaccharidoses.



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### HEATHER FLANAGAN-STEET, PH.D.

Heather Flanagan-Steet received her PhD from the Department of Molecular, Cellular and Developmental Biology at the University of Colorado-Boulder in 2001. Her thesis work on growth factor regulation of muscle myogenesis sparked a life-long interest in mechanism controlling tissue morphogenesis. During her post-doctoral training in the laboratory of Dr. Joshua Sanes at Washington University in St. Louis, she continued to pursue problems of early embryogenesis answering several outstanding questions about the coordinated development of neuromuscular synapses. During this time Dr. Flanagan-Steet learned the power of the zebrafish system to study early development and honed her skills in high-resolution microscopy. Her interest in the pathogenic mechanisms underlying lysosomal disease has emerged through a long-time collaboration with her husband, Dr. Richard Steet. Their work - which centers around the investigation of MLLI-associated cartilage and cardiac pathogenesis using zebrafish - continues at the Complex Carbohydrate Research Center at the University of Georgia.



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### IDA ANNUNZIATA, PH.D.

Ida Annunziata graduated with a degree in Biology at The University Federico II of Napoli, Italy and completed her doctorate degree in Medical Genetics in 2005. Since the early stages of her scientific career she has been interested in understanding the molecular bases underlying the severe and systemic manifestations in lysosomal storage disorders (LSDs). LSDs have been the focus of Dr. Annunziata's work during her pre- and post-doctoral years. In the laboratory of Dr. Alessandra d'Azzo, she has focused on the understanding of the molecular causes of neurodegeneration in the mouse models of two LSDs, GM1-gangliosidosis caused by deficiency of the enzyme  $\beta$ -galactosidase, and sialidosis, caused by deficiency of the lysosomal neuraminidase 1 (NEU1). Both projects have posed distinctive and interesting challenges that allowed Dr. Annunziata to broaden her knowledge on specific aspects of pathogenesis associated with these pediatric LSDs that are likely representative of other adult neurodegenerative conditions. In particular, the lab has recently discovered an unprecedented link between the enzyme NEU1 and Alzheimer's disease (AD). It was shown, in these studies that deficiency of NEU1 is a predisposing factor for AD and, most importantly, increasing the levels of NEU1 in a mouse model of AD ameliorates disease pathology and reduces the number of toxic plaques characteristic of the disease.

Lately, Dr. Annunziata has been interested in understanding how NEU1 is regulated. If this project will identify factors that control NEU1 lysosomal function. It will possible to use them to reactivate NEU1 residual activity particularly in Type I sialidosis.



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### 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, Mucopolipidosis 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.



### JULIA TARAVELLA

Julia Taravella, MS, ME, PE has a full time job in one of the Fortune 500 companies as a project technical lead and spends all her free time with kids and family and volunteering as an Executive Director of Rare Trait Hope Fund. The organization mission is to fund the development of a cure for Aspartylglucosaminuria (AGU).



### KATHERINE PONDER

Katherine P. Ponder is a professor in the Department of Internal Medicine at Washington University in St. Louis. She received a Bachelor's of Science from Stanford University in 1979, and a medical degree from Washington University in St. Louis in 1983. She was an intern in internal medicine at Parkland Hospital in Dallas, Texas, and then did post-doctoral training with Dr. Joan Steitz at Yale University and then with Dr. Savio Woo at Baylor College of Medicine.

Her research has focused on using gene therapy to treat hemophilia and mucopolysaccharidosis (MPS). Her laboratory has shown that neonatal intravenous injection of a gamma retroviral vector can result in stable expression of b-glucuronidase (GUSB) in serum for up to 11 years in MPS VII dogs, which results in prolonged survival and reduced orthopedic, cardiovascular, and other manifestations due primarily to secretion of enzyme modified with M6P by transduced liver cells. However, this approach fails to prevent disease in cartilage, which is likely due to poor diffusion of enzyme from blood. In addition, enzyme activity was low in brain, which was likely due to inefficient transfer across the blood brain barrier. A focus of recent work has been to deliver AAV or retroviral vectors to the brain in order improve expression and reduce neurological manifestations.

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### KARIN ÖLLINGER

Karin Öllinger received her MS degree from the University of Linköping in 1986 and her PhD degree in Pathology 1992 from the same university. She was a guest researcher at Griffith University, Southport, Australia in 2002.

Currently she is a Professor of Experimental Pathology and head of the Division of Cell Biology at the University of Linköping. Her present research interests include lysosomal function in normal physiology as well as in cancer and neurodegeneration.

Karin Öllinger has served in advisory panels at the Swedish Research Council and is member of the University board at Linköping University. Karin Öllinger has received scientific awards including the small Fernström Price from the University of Lund and she has authored more than 70 peer-reviewed articles, reviews and book-chapters.

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### 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.

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### MARC PATTERSON, M.D., FRACP, FAAN, FANA

Marc Patterson was born and educated in Australia, and trained in neurology, child neurology and neurometabolic disease at the University of Queensland, at Mayo Clinic, and at NINDS/NIH, the last mentioned under the guidance of Roscoe Brady, MD. He is currently Professor of Neurology, Pediatrics and Medical Genetics, Chair of the Division of Child and Adolescent Neurology, and Director of the Child Neurology Training program at Mayo Clinic, having previously served as Professor and Director of Pediatric Neurology at Columbia University in New York. 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 has served in a number of positions in the Child Neurology Society, American Academy of Neurology, American Board of Psychiatry and Neurology and American Neurological Association. Professor Patterson has served on the editorial board of Neurology, on the oversight committee of Annals of Neurology and is currently an Editor for the Journal of Inherited Metabolic Disease. He became Editor-in Chief of the Journal of Child Neurology on January 1st, 2014, and subsequently Editor-in-Chief of its open-access sister journal, Child Neurology Open.

His research and practice 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 more than 180 peer-reviewed papers and book chapters. He has presented widely through the United States and internationally, both to professional and lay organizations. Dr Patterson has received funding support from NIH, industry and private foundations.

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**MARK HASKINS, V.M.D., PH.D.**

Dr. Haskins has established the Mucopolysaccharidosis (MPS) I, IIIB, VI, MPS VII, Mucopolysaccharidosis 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 recherche 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

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**MICHAEL BECK, M.D.**

**Education and Scientific Training**  
1969-1972: Medicine, J.W. Goethe University of Frankfurt/Main

1975: M.D., Institute of Biochemistry, University Frankfurt/Main  
Subject: Metabolic pathways and transport phenomena in bacteria

1972-1978: Training in Paediatrics at the Children's Hospital of the University of Frankfurt/Main

1979-1980: Training in Genetics at the Institute for Human Genetics, University of Frankfurt/Main

**Work experience**

1980-2013: Paediatrician at the Children's Hospital University of Mainz

1993-2013: Senior consultant at the Children's Hospital University of Mainz  
Head of the Biochemical Laboratory at the Children's Hospital University of Mainz

1993: Professorship in Paediatrics.  
Subject of the Habilitation: Proteoglycan Metabolism in Skeletal Dysplasias

2002 - 2013: Head of the Department for Lysosomal Storage Disorders at the Children's Hospital University of Mainz (Villa Metabolica)

2014: Professor Emeritus at the Institute of Human Genetics at the University of Mainz

**Further relevant activities**

1983: Training in Biochemistry at the Institute of Biochemistry of the University of Münster (Head: Prof. Dr. K. von Figura).

Subject: Proteoglycan metabolism in Genetic Diseases

1987: Research on Metabolism of Chondrocytes in Genetic Skeletal Dysplasias (University of Texas, Houston TX)

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1993: Organization of the 3rd International Symposium on Mucopolysaccharidoses and Related Diseases (in Essen)

2002-2013: Principal Investigator in Clinical Trials (Enzyme Replacement Therapy in Fabry disease, MPS I, MPS II, MPS VI, MPS IV, Pompe's disease)

Study on Natural History of Mannosidosis, (Project of the 6th European Frame Programme).

Study on Enzyme Replacement Therapy in Mannosidosis (Project of the 7th European Frame Programme)

2004: Organization of the 8th International Symposium on Mucopolysaccharidoses and Related Diseases (in Mainz)

**Further relevant activities**

1983: Training in Biochemistry at the Institute of Biochemistry of the University of Münster (Head: Prof. Dr. K. von Figura).  
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1993: Organization of the 3rd International Symposium on Mucopolysaccharidoses and Related Diseases (in Essen)

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2004: Organization of the 8th International Symposium on Mucopolysaccharidoses and Related Diseases (in Mainz)



### MICHAEL WHYTE, M.D.

Michael P. Whyte, M.D. is Professor of Medicine, Pediatrics, and Genetics at the Washington University School of Medicine, a staff member of Barnes-Jewish Hospital and St. Louis Children's Hospital, and Medical-Scientific Director at the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospital for Children in St. Louis, Missouri.

Dr. Whyte earned his M.D. degree at Downstate College of Medicine, State University of New York, Brooklyn, New York and then had internship and residency training in Internal Medicine at Bellevue Hospital in New York City. After two years as Clinical Associate at the National Institutes of Health, Bethesda, Maryland, he did his fellowship in the Division of Bone and Mineral Diseases and joined the medical faculty of the Washington University School of Medicine, St. Louis.

Dr. Whyte's research interests include especially the cause, outcome, and treatment of heritable disorders of bone and mineral metabolism in children and adults. Included are genetic forms of rickets such as hypophosphatasia and X-linked hypophosphatemia, brittle bone diseases like osteogenesis imperfecta, conditions that cause dense bones such as osteopetrosis, and disorders of accelerated skeletal turnover including juvenile Paget's disease. Laboratory investigations include searches for the underlying mutated genes of new disorders. Phenotype/genotype correlations aim to better understand the pathogenesis of established conditions. Bone-targeted alkaline phosphatase replacement therapy is being evaluated for children and teenagers with hypophosphatasia. The Research Center at Shriners Hospital serves as a national resource for the diagnosis, treatment, and investigation of disorders of bone and mineral metabolism and skeletal dysplasias in children. Dr. Whyte has authored or coauthored more than 300 scientific papers or book chapters concerning these disorders.

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### NICK PIETRIS

Dr. Pietris is a pediatric cardiologist who specializes in non-invasive cardiac imaging and cardiopulmonary exercise stress testing. After completing his undergraduate and medical studies (Bachelor of Science in Biochemistry, SUNY Stony Brook and Medical Doctorate, SUNY Buffalo) he completed a residency in pediatrics and fellowship in pediatric cardiology at Yale New Haven Hospital. After completing his primary fellowship at Yale, he continued his training and research in advanced pediatric cardiac imaging within the Children's Heart Program at the Medical University of South Carolina (MUSC). Dr. Pietris' academic interests include non-invasive cardiac imaging, cardiac manifestations of genetic diseases in addition to exploring the function and potential applications of stem cell therapy in congenital heart disease.

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### PIRKKO HEIKINHEIMO

Pirkko Heikinheimo graduated in biochemistry from University of Turku in 1997. During her postdoctoral period she worked in University of Miami, US, University of Turku, Finland, and in University of Tromsø, Norway. In 2003 she established her own research group in University of Helsinki, concentrating on structural biology of lysosomal proteins, especially the lysosomal  $\alpha$ -mannosidase. From 2010 on, Pirkko Heikinheimo had worked in Department of Biochemistry at University of Turku. During the term 2014-2015 Pirkko Heikinheimo has been in a teacher-training program for high school and college students.

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**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.

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**ROSA PUERTOLLANO, NIH/NHLBI, PH.D.**

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Rosa Puertollano received a BS and a MS in Biochemistry and Molecular Genetics from the Universidad Autonoma de Madrid, Spain, in 1994, and a Ph.D. in Biochemistry and Molecular Biology from the Consejo Superior de Investigaciones Cientificas (CSIC), Spain, in 1999. Following her graduation she undertook a postdoctoral fellowship at the National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH) under the supervision of Dr. Juan Bonifacino. In 2004, Dr. Puertollano joined the National Heart, Lung, and Blood Institute (NHLBI, NIH) as a Principal Investigator where she is the Chief of the Laboratory of Protein Trafficking and Organelle Biology.

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**RICHARD MORBEY**

Currently an Orthopaedic Consultant Surgeon specializing in Upper Limb Surgery at Tauranga Public Hospital and Grace Orthopaedic Centre Tauranga, New Zealand. Graduated in Medicine at Auckland University then trained in Orthopaedic surgery on the NZ Orthopaedic training program as part of the Royal Australasian College of Surgeons. Undertook Hand and Shoulder Fellowships at Royal North Shore Hospital, Sydney, Australia and a Hand Fellowship at the Derbyshire Royal Infirmary, Derby UK. Worked as Consultant Hand Surgeon at Middlemore Hospital Hand Surgery Department in Auckland before moving to Tauranga in 1996

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**SARA CATHEY, M.D.**

Dr. Cathey is a clinical geneticist based in the Charleston Office of the Greenwood Genetic Center (GGC). Her special areas of interest include birth defects, intellectual disabilities, and lysosomal diseases. She is recognized internationally as a leading clinical expert in the study of Mucopolysaccharidosis II and III. Dr. Cathey is principal investigator of the Longitudinal Studies of the Glycoproteinoses, a natural history study of these disorders. Her interest in these conditions was ignited by her patients, their families, and the unmet need for effective therapies. Since 2006 Dr. Cathey and GGC have partnered with ISMRD to evaluate patients with these rare conditions at special clinics in the United States, Australia, and New Zealand. Dr. Cathey is certified by both the American Board of Pediatrics and the American Board of Medical Genetics.

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### SCOTT GARMAN

Scott Garman is a structural biologist with an interest in lysosomal storage diseases. He was an undergraduate in chemistry at Princeton University, trained as a graduate student in biophysics at Harvard University, and then did post-doctoral studies at Northwestern University. At Northwestern, Garman determined the structures of the human high-affinity IgE receptor, both alone and in complex with its IgE antibody ligand. At the National Institutes of Health, Garman began work on the structural biology of lysosomal enzymes, publishing the structure of human alpha-galactosidase A, the enzyme that is defective in Fabry disease patients, in 2004. After moving to the University of Massachusetts Amherst, Garman's lab has continued work on human lysosomal enzymes, publishing the first structures of alpha-N-acetylgalactosaminidase and GALNS, the enzymes defective in Schindler disease and mucopolysaccharidosis IV A respectively. He is currently an Associate Professor in the Department of Biochemistry and Molecular Biology at the University of Massachusetts Amherst. In 2009, Garman won a Distinguished Teaching Award, the highest teaching honor conferred by the University of Massachusetts Amherst. In 2015, he received the College of Natural Sciences Outstanding Research Award.

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### STEVEN GRAY, PH.D.

Dr. Gray is Professor of Neuroscience, Pathology and Neurology and Director of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center at the Albert Einstein College of Medicine. His research interests began during his early training in Comparative Medicine and Neuroscience and involved animal models of GM1 and GM2 gangliosidosis (Sandhoff disease). His laboratory today is focused on defining the pathogenesis of numerous endosomal-lysosomal system disorders including Niemann-Pick types A and C, the gangliosidoses, Farber, MLIV, MPS IIIA and the NCLs, as well as the recently discovered endosomal disease, Christianson syndrome. Of particular focus are disease-induced changes in endocytic, autophagic and salvage pathways and their impact on dendritic and axonal integrity and the neuronal connectome. Dr. Gray's lab has also been in the forefront of therapy development for lysosomal disorders, including the first and presently only approved therapy for Niemann-Pick type C disease. Dr. Gray was a co-founder of the newly developed Gordon Research Conference on Lysosomal Disease and is an active member of the scientific advisory boards for numerous lysosomal disease organizations.

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### STEVEN WALKLEY, D.V.M., PH.D.

Dr. Walkley is Professor of Neuroscience, Pathology and Neurology and Director of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center at the Albert Einstein College of Medicine. His research interests began during his early training in Comparative Medicine and Neuroscience and involved animal models of GM1 and GM2 gangliosidosis (Sandhoff disease). His laboratory today is focused on defining the pathogenesis of numerous endosomal-lysosomal system disorders including Niemann-Pick types A and C, the gangliosidoses, Farber, MLIV, MPS IIIA and the NCLs, as well as the recently discovered endosomal disease, Christianson syndrome. Of particular focus are disease-induced changes in endocytic, autophagic and salvage pathways and their impact on dendritic and axonal integrity and the neuronal connectome. Dr. Walkley's lab has also been in the forefront of therapy development for lysosomal disorders, including the first and presently only approved therapy for Niemann-Pick type C disease. Dr. Walkley was a co-founder of the newly developed Gordon Research Conference on Lysosomal Disease and is an active member of the scientific advisory boards for numerous lysosomal disease organizations.

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### STUART KORNFELD, M.D.

Dr. Kornfeld received his M.D. from Washington University in St. Louis where he is currently the David C. and Betty Farrell Professor of Medicine. The major focus of his research is protein trafficking and organelle biogenesis. Specifically, he studies 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 the lysosomal storage disorders mucopolysaccharidosis II and III. Most recently his lab has been analyzing the consequences of patient mutations on the function of the enzyme UDP-GlcNAc:lysosomal enzyme N-acetylglucosamine-1-phosphotransferase which mediates the initial step in the generation of the phosphomannosyl residues on lysosomal acid hydrolases. In related work his lab has been studying mice with disruptions in the two genes that encode the subunits of phosphotransferase to follow the development of pathologic changes in various tissues.

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Dr. Kornfeld is a member of the National Academy of Sciences and has received a number of awards for his scientific contributions. The research is supported by a NIH grant with Merit Status and by a grant from the Gandhi Foundation.



### TERRA BARNES

I am currently a postdoctoral research associate in the lab of Timothy Holy at Washington University School of Medicine. I specialize in the neural correlates of complex motor behavior. I have spent the last several years studying one complex motor behavior: mouse vocalizations. I study the vocalizations of mouse models of stuttering and mucopolidosis. I received my Ph.D. from MIT in the laboratory of Ann Graybiel where I studied the spatial and temporal firings of neurons in the basal ganglia. My publication in Nature described a unique "explore-exploit" pattern of neuronal learning that has proven to be a significant step forward in our understanding of the physical basis of learning in mammals.

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### THOMAS BRAULKE, PH.D.

Thomas Braulke obtained his PhD in Neurochemistry from the University of Leipzig in Germany. He is professor of Biochemistry at the University Medical Center Hamburg-Eppendorf, Germany, and has a long standing interest in the field of lysosomes and lysosomal storage disorders. In 1989 he became a group leader in the Institute of Biochemistry of Prof. Kurt von Figura at the University of Goettingen, and established a new Department for Biochemistry at the Children's Hospital in Hamburg 1999. His laboratory has a solid experience in a variety of molecular and cell biological techniques as well a significant expertise in protein chemistry and mouse analysis. His research is focused on the biogenesis of lysosomes and pathogenic mechanisms underlying lysosomal storage diseases. During the past 10 years, neuronal ceroid lipofuscinoses (NCL, Batten diseases) and mucopolidosis type II (MLII) and III were of his particular interest. His group has identified the gene defect causing the partial or complete loss of mannose 6-phosphate residues on lysosomes enzymes in MLII/III. The analyses of the MLII mouse model provided new insights into pathogenic alteration of the brain, skeleton and the immune system. His work is financially supported by the German Research Foundation, the European Community and the National MPS Society.

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### 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.

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### WILLIAM SLY, M.D.

William S. Sly, M.D., directed the Division of Medical Genetics at Washington University for 20 years, after which he chaired the Department of Biochemistry and Molecular Biology at Saint Louis University for 26 years, ending in 2010. He became Emeritus Professor in 2014. 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 also 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. For this work, he was inducted into the National Academy of Sciences in 1989. He has also received awards from the National (US) and International MPS Societies. He currently collaborates with Ultragenyx and others on developing ERT for MPS VII.



# Delegates

Parents			
Last Name	First Name	Disorder	Country
Adkins	Patricia	Mucopolipidosis II - Parent (ISMRD Board Member)	USA
Amour	Sherrie	Mucopolipidosis III - Parent	USA
Andrews	Jane	Mucopolipidosis II - Parent	USA
Armand	Stephanie	AGU/ Parent	France
Barham	Linda	Mucopolipidosis III - Parent	USA
Barham	Greg	Mucopolipidosis - Family Member	USA
Barsotti	Jamie	Mucopolipidosis III - Parent	USA
Barsotti	William	Mucopolipidosis III - Parent	USA
Bell Broersma	Judy	Carer	New Zealand
Bloomberg	Mary	AGU - Parent	USA
Cardenas	Maria Elena	Mucopolipidosis II/III - Parent	USA
Crompton	Denise	Mucopolipidosis II/III - Parent	USA
Crompton	Bob	Mucopolipidosis II/III - Parent	USA
Faerdy	Dana	Alpha Mannosidosis - Parent	USA
Faerdy	Travis	Alpha Mannosidosis - Parent	USA
Feagle Sounart	Deborah	Alpha Mannosidosis - Guardian - Sister	USA
Forman	John	Alpha Mannosidosis - Parent (ISMRD Board Member)	New Zealand
Gertner	Patricia	Sialidosis - Parent	USA
Haggett	John	Mucopolipidosis II/III - Parent	USA
Haggett	Brenda	Mucopolipidosis II/III - Parent	USA
Huneault	Perry	Sialidosis - Parent	Canada
Irvine	Emmeline	Mucopolipidosis III - Carer	United Kingdom
James	Jackie	Mucopolipidosis III - Parent (ISMRD Board Member)	USA
James	Bret	Mucopolipidosis III - Parent	USA
Jamil	Shirley	Mucopolipidosis III - Parent	United Kingdom
Kester	Susan	Mucopolipidosis III - Parent (ISMRD Board Member)	USA
Kimmet	Kevin	Mucopolipidosis II/III - Parent	USA
Kimmet	Mary	Mucopolipidosis II/III - Parent	USA
King	Kathleen	Alpha Mannosidosis - Parent	USA
Klein	Terri	Mucopolipidosis III - Parent	USA
Laca	Ferando	Family Member	USA
Mackay	Colin	Alpha Mannosidosis - Parent	Canada
Mackay	Kathy	Alpha Mannosidosis - Parent	Canada
Mikuta	Donatas	Alpha Mannosidosis - Parent	United Kingdom
Mikutiene	Gintare	Alpha Mannosidosis - Parent	United Kingdom
Noble	Jenny	Mucopolipidosis III - Parent - (ISMRD Board Member)	New Zealand
Noble	Paul	Mucopolipidosis III - Parent	New Zealand
O'Connor	John	Mucopolipidosis II - Parent	Ireland

O'Connor	Emma	Mucopolipidosis II - Parent	Ireland
Paisley-Dew	Carolyn	Fucosidosis - (ISMRD Board Member)	Australia
Potts	Nicole	Mucopolipidosis III - Parent	USA
Roll	Birthe	Mucopolipidosis III - Parent	Norway
Roll	Truls	Mucopolipidosis III - Parent	Norway
Ryan	Ida	Sialidosis - Parent	Canada
Schleter	Mike	Mucopolipidosis III - Parent	USA
Sibert	Elizabeth	Mucopolipidosis III - Parent	USA
Simp	Ada	Fucosidosis - Parent	USA
Simpson	Jennifer	Mucopolipidosis III - Parent	Canada
Sounart	Michael	Alpha Mannosidosis - Family Member	USA
Stark	Mark	Alpha Mannosidosis - Parent (President ISMRD)	USA
Taravella	Julia	AGU - Parent	USA
Taravella	Jody	AGU - Parent	USA
Thomas	Sheldon	Mucopolipidosis III - Parent	USA
Thomas	Starla	Mucopolipidosis III - Parent	USA
Thompson	Holly	Mucopolipidosis II/III - Parent	USA
Vergara	Jesus	Fucosidosis - Parent	USA
Webb	Sylvia	Mucopolipidosis II/III - Parent	Australia
Webb	Charles	Mucopolipidosis II/III - Parent	Australia
Sowers	David	Mucopolipidosis III - Parent	USA
Gilbert	Charlotte	Mucopolipidosis III - Parent	USA

## Affected Children

Andrews	Andre	ML II	USA
Bloomberg	Karin	AGU	USA
Burgess	Sarah	ML III	United Kingdom
Cardenas	Sergio	ML II/III	USA
Feagle	Rebecca	Alpha Mannosidosis	USA
Forman	Tim	Alpha Mannosidosis	New Zealand
Gertner	Amanda	Sialidosis	USA
Haggett	Zach	Mucopolipidosis II/III	USA
Huneault	Tyler	Sialidosis	Canada
Incardona	Hermance	AGU	France
James	Anna	ML III	USA
James	Savahna	ML III	USA
James	Dakota	ML III	USA
Jamil	Samuel	Mucopolipidosis III	United Kingdom
Kimmet	Andrea	Mucopolipidosis II/III	USA
Mackay	David	Alpha Mannosidosis	Canada





Nagy	Joey	ML III	USA
Noble	Hayden	ML III	New Zealand
Noble	Sarah	ML III	New Zealand
O'Connor	Aoibhe	ML II/III	Ireland
Potts	Tyler	Mucopolidosis III	USA
Roll	Pernille	ML III	Norway
Sibert	Mary	Mucopolidosis III	USA
Simp	Ava	Fucosidosis	USA
Simpson	Matt	ML III	Canada
Stark	Robert	Alpha Mannosidosis	USA
Taravella	Daniel	AGU	USA
Taravella	Alexander	AGU	USA
Teetor	Davin	Mucopolidosis III	USA
Thomas	Skylar	Mucopolidosis III	USA
Thompson	Madison	ML II/II	USA
Tice	Lonnie	ML III	USA
Webb	Grace	Mucopolidosis II/III	Australia
Webb	Tegan	Mucopolidosis II/III	Australia
Sowers	Hunter	Mucopolidosis III	USA

Siblings			
Carver	Jasmine	Sibling	USA
Barham	Bobby	Sibling	USA
Frison	Zion	Sibling	USA
Laca	Giovanni	Sibling	USA
Laca	Summer	Sibling	USA
Lynch	Liam	Sibling	Australia
O'Connor	Lauren	Sibling	Ireland
Roll	Stine	Sibling	Norway
Roll	Mia	Sibling	Norway
Shields	Chase	Sibling	Australia
Sibert	Robert	Sibling	USA
Simp	Amaya	Sibling	USA
Stark	Matthew	Sibling	USA
steet	Savannah	Sibling	USA
Steet	Lucas	Sibling	USA
Thomas	Sheridon	Sibling	USA
Tice	Chris	Sibling	USA
Tice	Sarah	Sibling	USA

Not for Profits and other Family Members			
Comardelle	Alla	Rare Trait Hope Fund	USA
Dow	Cathy	Family Member	USA
Gadawski	Micalla	Family Member	USA
Naess	Hanne	Family Member	Norway
Potts	Michael	Family Member	USA
Potts	Susan	Family Member	USA
Potts	Lawrence	Family Member	USA
Redon	Josette	Family Member	France
Roll	Vivi	Family Member	Norway
Stanton	Sue	Family Member	USA
Turner	Laurie	National MPS Society	USA
Webb	Caryl	Family Member	Australia
Webb	Christian	Family Member	Australia

Professionals/Industry			
Alegra	Taciane	Hospital De Clinicans de Porto Alegre	Brazil
Bedwell	David	University of Alabama	USA
Boonen	Marielle	University of Namur	Belgium
Cathey	Sara	Greenwood Genetic Centre	USA
Choi	Eun-Young	National Institute of Health	USA
De Pace	Raffaella	University Medical Centre Hamburg	Germany
Diwan	Abhinav	Washington University	USA
Doray	Balraj	Washington University Medical School	USA
Ferreira	Carlos	Children's National Medical Center/NIH	USA
Idol	Rachel	Washington University	USA
Koppaka	Vish	Ultragenyx Pharmaceutical Inc.	USA
Kornfeld	Stuart	Washington University	USA
Lee	Wang Sik	Washington University Medical School	USA
Liu	Lin	Washington University Medical School	USA
Markmann	Sandra	University Hospital Hamburg	Germany
Pollard	Laura	Greenwood Genetic Centre	USA
Ponder	Kathy	Washington University	USA
Simmons	Katrina	Greenwood Genetic Centre	USA
Smith	Elizabeth	Emory University	USA
Taylor	Rosanne	University of Sydney	Australia
Tikkanen	Ritva	University of Giessen, Germany	Germany

Invited Speakers			
Annunziata	Ida	St Jude Children's Hospital	USA
Barnes	Terra	Washington University	USA
Bartlett	AmyRuth	Counsellor	USA
Beck	Michael	University Medical Center, Langenbeckstrasse	Germany
Biffi	Alessandra	San Raffaele Telethon Institute for Gene Therapy	Italy
Bosch	Fatima	Universitat Autònoma Barcelona	Spain
Braulke	Thomas	University of Hamburg	Germany
Cuervo	Ana Marie	Albert Einstein University	USA
d'Azzo	Alessandra	St. Jude Children's Research Hospital	USA
Flannagan-Steet	Heather	Complex Carbohydrate Research Center	USA
Garman	Scott	University of MassAmherst	USA
Gray	Steven	University of North Carolina	USA
Haskins	Mark	University of Pennsylvania	USA
Heikinheimo	Pirkko	University of Turk	Finland
Horowitz	Lucia	Psychologist	USA
Kelly	Michael	Washington University	USA
Leroy	Jules	University Hospital and University Ghent	Belgium
Lund	Troy	University of Minnesota	USA
Malm	Dag	Tromso Center	Norway
Morbey	Richard	Consultant Surgeon, Tauranga Hospital	New Zealand
Ollinger	Karin	Linköping University	Sweden
Pan	Dao	Cincinnati Children's Hospital	USA
Patterson	Marc	Columbia University Medical Center	USA
Pietris	Nick	Professor of Pediatrics, University of Maryland	USA
Puertollano	Rosa	National Institute of Health	USA
Razani	Babak	Washington University	USA
Sly	Bill	St. Louis University	USA
Steet	Richard	Complex Carbohydrate Research Center	USA
Walkely	Steve	Albert Einstein University	USA
Whyte	Michael	Shriners Hospital for Children St. Louis	USA



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