5TH GLYCOPROTEINOSES INTERNATIONAL CONFERENCE

Rome, Italy
November 1-4 2017

Crossing oceans for a cure

EMBRACING INNOVATION ADVANCING THE CURE

PROGRAM
& ABSTRACTS

ISMRD is an internationally focused not-for-profit organization whose mission is to advocate for families and patients affected by one of the following disorders.

Alpha-Mannosidosis
Aspartylglucosaminuria
Beta-Mannosidosis
Fucosidosis
Galactosialidosis
Sialidosis (Mucolipidosis I)
Mucolipidosis II, II/III, III alpha/beta
Mucolipidosis III Gamma
Schindler Disease

5TH GLYCOPROTEINOSES INTERNATIONAL CONFERENCE

ROME, ITALY NOVEMBER 1-4 2017

EMBRACING INNOVATION ADVANCING THE CURE

ISMRD would like to say *a very special thank you* to the following organizations and companies who have very generously given donations to support the 5th International Conference on Glycoproteinoses.

ultragenyx pharmaceutical

SANOFI GENZYME

EVERYLIFE FOUNDATION FOR RARE DISEASES

Amicus Therapeutics

THE WAGNER FOUNDATION

ISMRD is *very grateful for all the help and support* that Symposia has given us in the organization of our Conference on-the-ground support in Rome.

symposia

Contents

Welcome to Rome!

On behalf of ISMRD, I would like to welcome you all to the Fifth Glycoproteinoses International Conference on **'Embracing Innovation and Advancing the Cure'**.

ISMRD is thrilled to bring our International Conference to Europe allowing us to connect with families, researchers, clinicians, support groups and others who work in the field of rare diseases. But, more importantly to help make the invaluable connections for families who perhaps have never met another family with their particular disease.

Over the next few days you will have the opportunity to learn about the advancements toward therapies for some of these diseases. You will hear from families about what it's like to live with one of these very rare conditions, and hear about the exciting advances towards Enzyme Replacement Therapy and Gene Therapy.

It takes many hours and hard work to bring together a meeting of this nature. I would like to thank our Primary Investigator Alessandra d'Azzo and her Scientific Committee who have put together a really strong scientific program with some amazing speakers from around the world.

Of course, our conference would not take place without significant charitable donations. I would like to thank the following companies and foundations, **Ultragenyx**, **EveryLife Foundation**, **Sanofi/Genzyme**, **Amicus** and **The Wagner Foundation**. I would also like to extend our very grateful thanks to Symposia who are event planners, who have worked alongside us here in Rome and have helped you check in at registration. They will be on site throughout the meeting offering support and answering any questions you may have.

To the families who are a part of the conference: welcome! It can be a lonely journey when you are told your child has a very rare genetic condition, especially when you might be the only family for miles around! These meetings help make all those important connections, creating a network of support, information and knowledge. I know there will be some lifelong friendships made this weekend. To families who have been to our meetings in the past please reach out to those who are new. I hope over the next few days you will have the confidence to approach the researchers and clinicians attending this meeting and ask all your questions. I know from experience that they look forward to this aspect of the conference.

My hope for each family attending is that you will leave this conference knowing that you have an ISMRD family that stands behind you, and that you are not alone in this journey.

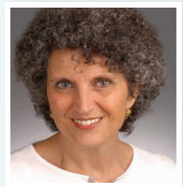
Jackie James
PRESIDENT ISMRD

On behalf of the Scientific Committee of ISMRD, it is my honor and great joy to welcome the patients, families, clinicians, and scientists who have traveled to Roma to attend the Fifth International Conference on Glycoproteinoses. This is the first ISMRD conference to be held in Europe. We changed the venue of this gathering to raise global awareness of these rare lysosomal disorders and increase the visibility of ISMRD as a family-centric organization that not only supports patients and their families but also funds scientific research and meetings on glycoproteinoses worldwide.

We designed this year's scientific program to bring together basic scientists and clinicians with patients and their families to share their latest discoveries in the areas of pathophysiology, preclinical therapy development, and clinical trials for these diseases. Patients and their family members have been included in the program to offer a unique opportunity to young researchers to learn first-hand about the experiences, challenges, and concerns of patients with glycoproteinoses and their expectations for the future.

Our vision for this conference is that it will stimulate the exchange of ideas, encourage new collaborations among investigators and clinicians with different expertise, spark interest in these diseases among postdoctoral research fellows and graduate students, strengthen connections among affected families around the world, and foster national and international partnerships to advance therapies for affected children and adolescents.

Together, we will keep advancing treatment and advocating for patients and families affected by these disorders.



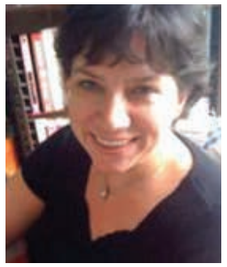
Enjoy the conference!

Alessandra d'Azzo Ph.D.
CHAIR SCIENTIFIC 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



Jackie James
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Vice President/Admin
New Zealand

John Forman
Vice President/Research
New Zealand

Mark Stark
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United States

Carolyn Paisley-Dew
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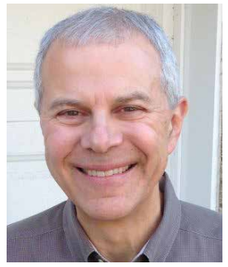


Paul Wagner
United States

Juanita Van Dam
Australia

ISMRD ADVISORY BOARD

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

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

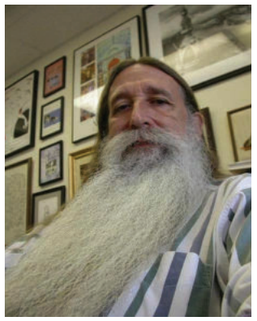
Barbara Burton, M.D.
Children's Memorial Hospital, Chicago, USA

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

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

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

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



Mark Haskins, V.M.D., Ph.D.
University of Pennsylvania Veterinary 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 go to Registration during Welcome Reception on 1st November to get your presentations loaded onto the computer prior to the commencement of the conference.

If you missed the above please go to the Registration desk between 7:30am and 8:00am, or see 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.

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 is thrilled to have the support of Symposia. Their staff are multilingual and are available to answer any questions you may have about the meeting.

ISMRD Board members are also available to help you.

CATERING

Welcome Reception:
1st November 6:30pm - 8:30pm
Buffet style food will be available

Breakfast is included in your Accommodation:
Go to the Sapori Dal Mondo Restaurant

Conference Breaks:
Tea, coffee and snacks will be served in the Conference Foyer

Lunch:
Lunch will be served in the Sapori Dal Mondo Restaurant at the International cooking stations.

REGISTRATION DESK TIMES

Wednesday 1st November
4:30pm - 6:30pm

Thursday 2nd November
7:30am - 4:30pm

Friday 3rd November
8:00am - 12noon

ISMRD Conference Functions

WELCOME RECEPTION

Wednesday 1st November

Time: 6:30pm – 8:30pm

Room: Foyer of the Conference Center

Drinks: A cash drinks station is available for all drinks.

Don't miss a great opportunity to meet your colleagues, meet old friends and make new ones before the conference begins at 8:30am the next day. An evening of local food and wine not to be missed.

AWARDS DINNER

Friday 3rd November

Time: 6:30pm for seating at 7pm

Room: The Conference Center

Join us for one of the highlights of our conference, this year's Awards Dinner will be something a little special.

Pre-dinner drinks will be available at a cash drinks station before the commencement of a 3-course dinner. The food, wine and entertainment promise to give you a great night of fun and relaxation.

Eating Out in Rome

The Restaurants below are a small sample of what is available within a few kilometres of the A. Roma LifeStyle Hotel. However if you want to go further into the city please ask the Hotel Staff to recommend a restaurant to you.

You may find it easier to catch a taxi to your destination. You can expect to pay approximately €20 per trip, depending on your destination.

BAR VITTORIA

5 minute walk from A.Roma Lifestyle Hotel

Piazza Biagio Pace 6,
00164 Rome
Phone 06 6615 7531

REVIEW: *"We stayed at the A.Roma Hotel and ate here most nights. The food is very good value and the service is fantastic! Always a good sign when a place is frequented by local residents as is the case here. Really added to our enjoyment of a great week in Rome. Thanks."*

RISTORANTE COUSINE RESTAURANT

5 minute walk from A.Roma Lifestyle Hotel

Via Camillo Serafini 47,
00164 Rome
Phone 06 9259 9077

CUISINES: Italian, Pizza, Mediterranean

REVIEW: *"They make a good fresh cuisine, classic dishes prepared and presented well .... try."*

CASETTE DI CAMPAGNA

1.6km from A.Roma Lifestyle Hotel

Via di Affogalasino, 40,
00148 Rome
Phone 06 6574 3230

REVIEW: *"Great food, top quality service and beautiful location."*

OSTERIA PALMIRA

1.8km from A.Roma Lifestyle Hotel

Via Abate Ugone 29
Phone 06 5820 4298

CUISINES: Italian, Mediterranean

REVIEW: *"If you are considering Osteria Palmira, go! It has a great atmosphere, good service, great food and great value!"*

PERDINCIBACCO

2.1km from A. Roma LifeStyle Hotel

Via delle Fornaci 5,
00165 Rome
Phone 06 632 527

REVIEW: *"Delicious and inexpensive. The spaghetti with garlic and chilli was amazing. Antipasti misto was fab too."*

Suggested Tour Options

Enquires can be made at the hotel with the concierge.

The Coliseum

The Vatican

The Trevi Fountain

Pantheon

Borghese Art Gallery

"Rome is the city of echoes, the city of illusions, and the city of yearning."

Giotto di Bondone
(Italian painter and architect. Died 1337)

Scientific Program

DAY 2: NOVEMBER 2ND 2017		
Chair: Alessandra d'Azzo		
8:30am	Welcome and introduction to the meeting	*Jackie James - USA, Alessandra d'Azzo - USA*
8:45am	**Keynote Presentation:** Glycoproteins and Glycoprotein Storage Diseases - An Overview	*Stuart Kornfeld - USA*
9:30am	Cell Biology and Pathophysiology of Lysosomal Storage Diseases	*Fran Platt - England*
10:00AM MORNING BREAK		
Session 1 – Alpha Mannosidosis		**Chair: Dag Malm**
10:20am	a-Mannosidosis Historical and Current Aspects	*Dag Malm - Norway*
10:40am	Diagnosis and monitoring of patients with glycoproteinoses disorders by novel UPLC-MS/MS Oligosaccharide analysis	*Sara Cathey - USA*
11:00am	Lysosomal alpha Mannosidase and alpha Mannosidosis	*Tommaso Beccari - Italy*
11:20am	Hematopoietic Cell Transplant for Glycoproteinoses	*Troy Lund - USA*
11:50am	Long-term Efficacy and Safety of Velmanase Alfa (Human Recombinant alpha-mannosidase) Long-term Enzyme Replacement Therapy for Alpha-Mannosidosis	*Line Borgwardt - Denmark*
12:15pm	Enhanced Phosphorylation of Lysosomal Enzymes Mediated by an Engineered GlcNAc-1-phosphotransferase	*Balraj Doray - USA*
12:25pm	A Patient's View: Living with Mannosidosis - A shared presentation	*John Forman - New Zealand Dag Malm - Norway*
		Chair: Maurizio Scarpa
12:40pm	General Discussion: Engaging with families, patients, Clinicians, Geneticists, genetic counsellors on clinical and molecular diagnosis, clinical care person experience with individual cases, Therapies and Clinical biomarkers for assessing outcomes etc.	*Panelists: Christina Lampe, Rossella Parini, Sara Cathey*
1:00PM LUNCH		
		Chair: Stuart Kornfeld
2:00pm	Lysosomal membrane proteins and their functions	*Paul Saftig - Germany*
2:30pm	Efficacy of BMT and AAV – mediated therapy in Krabbe disease	*David Wenger - USA*
Session 2: Mucolipidosis II and III		
3:00pm	Mannose-phosphorylation in health and disease	*Thomas Braulke - Germany*
3:30PM BREAK		
3:50pm	Activity Base Profiling In Live Zebrafish Reveals TGFß Regulation of Cathepsin Activation During MLII Pathogenesis	*Heather Flannagan-Steet - USA*
4:10pm	Functional Analysis of GNPTAB and GNPTG Null Cells Identifies Reactive Oxygen Species (ROS)-Dependent Increases in c-Met Activity	*Richard Steet - USA*
4:30pm	Zebrafish model of lysosomal disorders associated with skeletal defects: Challenging an old paradigm of disease pathogenesis	*Enrico Moro - Italy*
5:00pm	A Natural History Study and AAV-mediated Gene Therapy Approach for Feline Mucolipidosis II	*Allison Bradbury - USA*
5:20pm	Coatomer participates in the Golgi localization of GlcNAc-1-phosphotransferase	*Lin Liu - USA*
5:30pm	A Patient's View: Living with ML II and ML III – a shared presentation	*ML II – Paul Wagner - USA ML III – Jenny Noble - New Zealand*
		Chair: Sara Cathey
5:50pm	General Discussion: Engaging with families, patients, Clinicians, Geneticists, genetic counsellors on clinical and molecular diagnosis, clinical care person experience with individual cases, Therapies and Clinical biomarkers for assessing outcomes etc.	*Panelists: Christina Lampe, Rossella Parini, Gepke Visser, Agata Fiumara, Elena Procopio*

DAY 3: NOVEMBER 3RD 2017		
		Chair: Generoso Andria
8:30am	Heat Shock Protein-based therapies as clinical candidates for sphingolipidoses	*Thomas Kirkegaard Jensen - Denmark*
Session 3: Sialidosis (ML I) and Galactosialidosis		
9:00am	Sialidosis (ML I) and Galactosialidosis: Historical and clinical overview	*Generoso Andria - Italy*
9:30am	Molecular pathophysiology in Sialidosis: Links to adult conditions of aging	*Alessandra d'Azzo - USA*
10:00am	Lymphatic pathway in glycoproteinoses	*Noelia Escobedo - USA*
10:20am	Factors regulating transcription of the lysosomal sialidase NEU1	*Ida Annunziata - USA*
10:40AM BREAK		

11:00am	Enzyme replacement therapy for galactosialidosis, Towards the Clinical Trial	*Vish Koppaka - USA*
11:20am	Myoclonus is a key symptom of the adult form of Sialidosis Type I	*Laura Canafoglia - Italy*
11:30am	Molecular diagnosis of glycoproteinoses	*Amelia Morrone - Italy*
11:50am	A Patient's View: Living with Sialidosis Type I	*Daniel Peach - New Zealand*
		Chair: Bruno Bembi
12:10pm	General Discussion: Engaging with families, patients, Clinicians, Geneticists, genetic counsellors on clinical and molecular diagnosis, clinical care person experience with individual cases, Therapies and Clinical biomarkers for assessing outcomes etc.	*Panelists: Camilo Toro, Andrea Dardis, Gepke Visser, Alice Donati, Sara Cathey, Laura Canafoglia, Agata Fiumara, Amelia Morrone*
12:40pm	Afternoon free for networking or taking one of the tour options in Roma	

AWARDS DINNER 6:00PM FOR 7:00PM FOR SEATING

DAY 4: 4TH NOVEMBER 2017

		Chair: Alessandra d'Azzo
8:30am	Epilepsy in Lysosomal Storage Diseases	*Renzo Guerrini - Italy*
9:00am	Intracerebroventricular cerliponase alfa for children with CLN2 disease: Interim results from an ongoing Phase 2 extension study	*Angela Schulz - Germany*
Session 4: Aspartylglucosaminuria, Fucosidosis, Schindler Disease		Chair: Alessandra d'Azzo
9:30am	Personalized therapy approaches for AGU	*Ritva Tikkanen - Germany*
10:00am	AAV-based therapy in aspartylglucosaminuria mice	*Xin Chen - USA*
10:30am	A Mouse Model for Fucosidosis	*Torben Lübke - Germany*
11:00AM BREAK		
11:20am	A Patient's View: Living with Fucosidosis	*Jean Leonard - England*
11:40am	ERN for metabolic disorders: An Overview	*Maurizio Scarpa - Germany*
12:10pm	GalNAcT/AGU double knockout mice experience accelerated disease over the single aspartylglucosaminuria mice	*Matthew Ellinwood - USA*
12:30pm	The genetic diagnosis: a long and complex case of Mucolipidosis III in Brazil	*Ida Schwartz - Brazil*
12:40pm	Meeting Summary	*Maurizio Scarpa - Germany*
1:00pm	Closing of Meeting	*Jackie James - President ISMRD*

Family Program

This year we are trying something a little different. Rather than having presentations in your workshops, we thought you would benefit from having round table discussions sharing information and asking all the questions you ever wanted to ask of the Professionals.

Please join the scientific meeting for the first part of the morning on day 2 and then see below when your particular workshop is scheduled.

DAY 2: NOVEMBER 2ND 2017		
8:30am	Welcome and introduction to the meeting	*Jackie James - USA, Alessandra d'Azzo - USA*
8:45am	Keynote Presentation: Glycoproteins and Glycoprotein Storage Diseases an Overview	*Stuart Kornfeld - USA*
9:30am	Cell Biology and Pathophysiology of Lysosomal Storage Diseases	*Frances Platt - England*
10:00AM MORNING BREAK		
Aspartylglucosaminuria Workshop		
10:20am	General Discussion	
	Research - What is the future - What can be done	
	Medical Management	
1:00pm	General Discussion Q&A	
Fucosidosis Workshop		Chair: Carolyn Paisley-Dew
10:20am	General Discussion	
	Research - What is the future - What can be done	
	Medical Management	
1:00pm	General Discussion Q&A	

DAY 3: NOVEMBER 3RD 2017		
Alpha Mannosidosis Workshop		Chair: Mark Stark
8:30am	Alpha Mannosidosis - An Overview	*Dag Malm - Norway*
	A Parents View: Bone Marrow Transplant	*Martin Woolley - England*
	Medical Management	
10:40AM MORNING BREAK		
	A Parents View: Living with Alpha Mannosidosis	*Mark Stark - United States*
12:30am	General Discussion and Q&A	

Mucolipidosis Workshop		Chair: Jackie James
8:30am	Mucolipidosis an Overview - Where are we at and what's new	*Sara Cathey - United States*
	Research - What is the future for ML, What can ML Families do to help	
	Medical Management	
10:40AM MORNING BREAK		
	Bone Disease and Pain Management - What is being done - What can be done	
	A Parent/Patient's View: Living with Mucolipidosis III	*Shirley Jamil - England*
12:30pm	General Discussion and Q&A	

DAY 4: NOVEMBER 4TH 2017		
Sialidosis Workshop		Chair: Daniel Peach
8:30am	Sialidosis - An Overview	
	Research - Where are we at?	
	A Patients View: Living with Sialidosis	*Faith Peach - New Zealand*
	Medical Management - An Overview	
10:00am	Origin and Treatment of Neurological Symptoms in Sialidosis	*Camilo Toro - United States*
12:30pm	General Discussion and Q&A	
Galactosialidosis Workshop		Chair: Daniel Peach
8:30am	Sialidosis - An Overview	
	Research - Where are we at?	
	A Patients View: Living with Sialidosis	*Faith Peach - New Zealand*
	Medical Management - An Overview	
10:00am	Origin and Treatment of Neurological Symptoms in Sialidosis	*Camilo Toro - United States*
12:30pm	General Discussion and Q&A	

Children's Program Information

IMPORTANT NOTICES FOR PARENTS

Parents are requested to have their children at the Child Care room by 8am in the Conference Center.

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 their 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 children will be having Pizza or lunch on day one. Additional snacks and drinks will be in their backpacks.

For children on special diets please make sure you include this in their packs.

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 in the childcare room before 8am to meet carers and then get those going out onto buses.

DAY 1: NOVEMBER 2ND 2017	
7:45am	Children to assemble at meeting point to meet their carers
8:45am	Children depart for the day's activities
9:00am	Luneur Park - Fun place for all ages. (If it is wet the children will go to the Zoologic Museum.)
12:00PM LUNCH	
4:00pm	Children return to the hotel
4:00pm - 5:30pm	Activities in the Children's Room until parents arrive at end of their session

DAY 2: NOVEMBER 3RD 2017	
7:45am	Children assemble at meeting point to meet their carers
8:45am	Children depart for 1/2 day activities
12:00pm	Close of day’s program
AFTERNOON FREE	

DAY 3: NOVEMBER 4TH 2017
Activities on site for today - Clown Therapy, and other activities to be arranged

Abstracts

Abstracts

GLYCOPROTEINS AND GLYCOPROTEIN STORAGE DISEASES - AN OVERVIEW

Stuart Kornfeld *(Keynote Presentation)*
Washington University School of Medicine

Cells synthesize numerous glycoproteins whose sugar chains serve a myriad of biologic roles. Eventually the glycoproteins are delivered to lysosomes by a variety of routes for degradation. Additional glycoproteins are internalized from outside the cell and sorted to lysosomes. In the acidic environment of the lysosome, the glycoproteins are degraded by a mixture of proteases and glycosidases. The catalytic pathway for the glycan degradation is highly ordered and bidirectional with the sequential removal of monosaccharides from both the reducing and the non-reducing ends of the glycans. The released sugars and amino acids are transported into the cytosol where they are reutilized.

Defects in any of the glycosidases involved in this process lead to an accumulation of the target oligosaccharides within the lysosome and a concomitant lysosomal storage disease. The current understanding of these pathways will be discussed.

NOV 2, 2017
Scientific Program
8.45 a.m

CELL BIOLOGY AND PATHOPHYSIOLOGY OF LYSOSOMAL STORAGE DISEASES

Frances Platt
University of Oxford

Although lysosomal diseases are "simple" monogenic disorders, the downstream consequences of the primary gene defect are highly complex at the cellular level, giving rise to convoluted pathogenic cascades. By unravelling the cell biology and pathophysiology of these enigmatic rare diseases, insights into fundamental cellular homeostasis are gained and novel approaches to treat these devastating diseases are discovered.

In this presentation, I will use Niemann-Pick disease type C (NPC) as an example to illustrate the complex pathophysiology of lysosomal diseases, the collateral damage arising in non-lysosomal systems in NPC cells and the emerging links between NPC and other rare and common diseases. I will also discuss why NPC therapeutics may hold promise for treating apparently unrelated human diseases.

NOV 2, 2017
Scientific Program
9.30 a.m

A-MANNOSIDOSIS HISTORICAL AND CURRENT ASPECTS

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 Tromsö, Norway (UiT) 1986-2010
- 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 Tromsö 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 "Tromsö 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 Tromsö 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 humans 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 Tromsö and focused his research on the design of clinical trials, understanding immune deficiency, characterizing psychiatric disease and developing non-invasive methods of detecting deposits in the brain.

NOV 2, 2017
Scientific Program
10:20 a.m

DIAGNOSIS AND MONITORING OF PATIENTS WITH GLYCOPROTEINOSES DISORDERS BY NOVEL UPLC-MS/MS OLIGOSACCHARIDE ANALYSIS

Taraka Donti, Rongrong Huang, Allison Cason, Laura Pollard, Tim Wood, Sara Cathey

Thin layer chromatography (TLC) has been the method used by clinical diagnostic laboratories to measure urinary free oligosaccharides (FOS) to identify patients with a variety of inborn errors of metabolism including the glycoprotein storage disorders, Pompe disease and more recently several congenital disorders of glycosylation. However TLC is not an optimal assay as it is not quantitative and lacks sensitivity and specificity. The interpretation of the banding patterns is subjective, creating variability from lab to lab. We developed a novel, rapid UPLC-MS/MS method to measure urinary FOS using reducing-end labeling. The relative concentration of nine disease-specific oligosaccharides is determined by comparison to the peak area of a single internal standard. As an initial validation, we analyzed 51 urine samples from a patient cohort encompassing eight LSDs: aspartylglucosaminuria (n=10), fucosidosis (n=4), alpha-mannosidosis (n=21), beta-mannosidosis (n=1), beta-galactosidase deficiency (n=8), Sandhoff disease (n=2), sialidosis (n=3) and galactosialidosis (n=2), which were collected as part of the Longitudinal Study of the Glycoproteinoses or through routine diagnostic testing. Age-specific normal ranges were developed using 110 samples from unaffected controls. An increased abundance of the disease-specific oligosaccharide was identified in all 51 affected individuals. When compared to age-matched controls, the elevations ranged from 5-2100 fold, with fucosidosis (average 1285-fold), sialidosis (average 426-fold), galactosialidosis (average 265-fold) and aspartylglucosaminuria (average 154-fold) showing the widest dynamic range. Urine samples from alpha-mannosidosis, fucosidosis and beta-mannosidosis patients who had been treated with hematopoietic stem cell transplantation had significantly lower oligosaccharide levels compared to untreated patients, indicating that this assay can be used to evaluate the efficacy of future treatments. We measured seven FOS in 75 urine samples from a cohort of ML patients. Three of the seven FOS species show significant elevations in ML patients as compared to controls suggesting they, collectively, can be used as a biomarker for this disease. We then stratified our patient cohort based on clinical classification of ML II, ML II/III, ML IIIą/ß. A statistically significant difference in the levels of these three FOS species was found between patients with ML II and ML II/III versus patients with ML IIIą/ß. Because these FOS levels correlate with clinical presentation of ML, we hypothesize these species and/or additional FOS may serve as good biomarkers to evaluate the efficacy of future therapeutics for ML.

NOV 2, 2017
Scientific Program
10.40 a.m

LYSOSOMAL ALPHA-MANNOSIDASE AND ALPHA-MANNOSIDOSIS.

Tommaso Beccari

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The lysosomal catabolism of glycoproteins is part of the normal turnover of cellular constituents and the cellular homeostasis of glycosilation. The catabolism of the N-linked glycoproteins has been studied more intensively than the digestion of other classes of glycoproteins because of the storage diseases (Glycoproteinoses) resulting from defect in their catabolism. The enzyme alpha-mannosidase occurs in multiple forms in human tissues and body fluid with multiple functions in glycoprotein metabolism. Lysosomal alpha-mannosidase with acidic pH optimum is ubiquitous in human tissues where it is expressed in two major forms, A and B that are the product of a single gene located on chromosome 19. Mutations in the gene encoding for alpha-mannosidase cause alpha-mannosidosis, an autosomal recessive disease, resulting in the accumulation of unprocessed mannose containing oligosaccharide material. This rare disease has an estimated incidence of 1/500.000 live births and clinically is divided into three subgroups. Over 140 alpha-mannosidosis causing mutations have been identified but only a minority of them have been characterised at the cell biological or molecular level. The mutation types that have been discovered in alpha-mannosidosis are insertions, deletions, missense, nonsense and splicing site mutations, duplications and inversions. The crystal structure of bovine MAN2B1 revealed that the enzyme consists of four domains: an N-terminal alpha/beta-domain, and three all-beta-domains. The N-terminal alpha/beta domain contains the active site. This structure provides a template for further biochemical studies of alpha-mannosidase, of lysosomal transport and it is the first step in understanding the human form of alpha-mannnosidosis in detail. Today the most promising therapy for this disease is the enzyme replacement therapy. To develop this strategy a mouse model for alpha-mannosidosis has been generated and a recombinant human alpha-mannosidase has been produced from Chinese-hamster ovary cells. Interestingly it has been shown that the recombinant enzyme, used in high dose, can cross the blood brain barrier.

NOV 2, 2017
Scientific Program
11.00 a.m

HEMATOPOIETIC CELL TRANSPLANT FOR GLYCOPROTEINOSES

Troy C. Lund MSMS PHD MD FAAP

The glycoproteinoses are comprised of a group of rare diseases characterized by defects in the cellular processing of carbohydrate-linked proteins. Examples are the mannosidoses (alpha- and beta-), fucosidosis, galactosialidosis, the mucolipidoses (ML II and III), and sialidosis. The defect in lysosomal degradation of glycoproteins causing buildup of unprocessed substrates results 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 stem cell sources has been used as a therapeutic treatment. The rationale thus: 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 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 outcome to possible disease stabilization and possible 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 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.

NOV 2, 2017
Scientific Program
11.20 a.m

LONG-TERM EFFICACY AND SAFETY OF VELMANASE ALFA (HUMAN RECOMBINANT ALPHA-MANNOSIDASE)

Line Borgwardt[1], Natalie Guffon[2], Yasmina Amraoui[3], Christine I. Dali[1], Linda De Meirleir[4], Mercedes Gil-Campos[5], Bénédicte Heron[6], Silvia Geraci[7], Diego Ardigò[7], Federica Cattaneo[7], Jens Fogh[8], J. M. P. Van den Hout[9], Michael Beck[10], Simon A. Jones[11], Anna Tylki-Szymanska[12], Ulla Haugsted[13], Allan M. Lund[1]

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Alpha-mannosidosis is a rare autosomal recessive disorder caused by mutations in *MAN2B1* encoding for the lysosomal enzyme alpha-mannosidase.

Lack of activity of alpha-mannosidase causes impaired glycoprotein degradation and cellular accumulation of mannose-rich oligosaccharides, which results in motor function impairment, physical disability, immunodeficiency, recurrent infections, psychiatric symptoms, intellectual disability, and skeletal abnormalities. Clinical presentation and severity of alpha-mannosidosis vary significantly among patients.

At present, no licensed therapeutic options are available.

Velmanase alfa (Lamazym or rhLAMAN) is a recombinant form of the human enzyme alpha-mannosidase, currently in development as enzyme replacement therapy for the treatment of alpha-mannosidosis. A total of 33 patients (19 pediatrics and 14 adults, age range from 6 to 35 years) were treated with Velmanase alfa for a period comprised between 12 and 48 months and assessed for serum oligosaccharides accumulation, physical endurance, motor proficiency, immunoglobulin G (IgG) profile, quality of life and cognitive ability outcomes.

The biological activity of Velmanase alfa was demonstrated by a significant and sustained clearance of serum oligosaccharides. A statistically significant benefit on patients' motor function was documented as progressive improvement from baseline in 3-Minute Stair Climb Test (3MSCT) and in 6-Minute Walking Test (6MWT). Improvements in the Bruininks-Oseretsky test of motor proficiency (BOT-2) were observed in the pediatric population. In addition, a consistent increase in serum IgG concentrations was also observed reverting clinically-relevant hypo-gammaglobulinemia when present. Safety and immunogenicity profile of long-term treatment with Velmanase alfa resulted favorable and compatible with the chronic administration of the product.

These results support the relevant benefit of treatment of alpha-mannosidosis patients with Velmanase alfa, especially when treatment is started early in the pediatric age.

NOV 2, 2017
Scientific Program
11:50 a.m

ENHANCED PHOSPHORYLATION OF LYSOSOMAL ENZYMES MEDIATED BY AN ENGINEERED GLCNAC-1-PHOSPHOTRANSFERASE

Lin Liu, Wang-Sik Lee, Balraj Doray, Stuart Kornfeld

The major form of treatment for a number of lysosomal storage diseases at the present time is Enzyme Replacement Therapy (ERT), although the efficacy of the treatment varies among the individual disorders. Part of the reason for this is that some of the lysosomal enzymes used for ERT are poorly phosphorylated, limiting binding by cell surface mannose 6-phosphate receptors and subsequent uptake. Currently these enzymes are produced at high levels by mammalian cells and depend on the endogenous GlcNAc-1-phosphotransferase to phosphorylate the mannose residues on their glycan chains. In this study, we show that co-expression of an engineered truncated GlcNAc-1-phosphotransferase α/β precursor and the lysosomal enzyme of interest in the producing cells resulted in markedly increased phosphorylation and cellular uptake of the secreted lysosomal enzyme. This method also results in the production of highly phosphorylated acid β-glucocerebrosidase, a lysosomal enzyme that normally has just trace amounts of this modification. Co-transfection with the wild-type GlcNAc-1-phosphotransferase α/β precursor also enhanced phosphorylation of a subset of lysosomal enzymes tested. We are presently testing the uptake and tissue distribution of the highly phosphorylated lysosomal acid a-mannosidase in mice.

NOV 2, 2017
Scientific Program
12:15 p.m

LYSOSOMAL MEMBRANE PROTEINS AND THEIR FUNCTIONS

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The lysosomal membrane was thought for a long time to primarily act as a physical barrier separating the luminal acidic milieu of lysosomes and lysosome-related organelles from the cytoplasmic environment. Meanwhile, it has been realized that unique lysosomal membranes play essential roles in a number of cellular events ranging from phagocytosis, autophagy, cell death, virus infection to membrane repair1-3. An overview about the most interesting emerging functions of lysosomal membrane proteins (LMPs) and how they contribute to health and disease will be provided. Their role in acidification, transport of metabolites and ions across the membrane, intracellular transport of hydrolases4, lipid transport5 and the regulation of membrane fusion events has been documented. Studies in patient cells, non-mammalian model organisms and knockout mice contributed to our understanding of how the different lysosomal membrane proteins affect cellular homeostasis, developmental processes as well as tissue functions. More than 150 integral LMPs have been identified6 but only for a minority of these proteins studies about their biochemistry and function has been reported. New experimental tools, such as electrophysiological recording of lysosomal currents and metabolite transport assays, new animal models as well as genetic studies are useful to fill the gap of knowledge about these fascinating and highly specialized proteins. Although a considerable gain of knowledge about the function of LMPs within the lysosomal membrane has attracted the attention of a wide field of cell biological researchers, we are only at the beginning to fully realize the complexity and molecular players and details of the events regulated by membrane proteins in the interface between the cytosolic and the lysosomal world.

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EFFICACY OF BMT AND AAV-MEDIATED THERAPY FOR KRABBE DISEASE

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Krabbe disease is an autosomal recessive disorder resulting from defects in the lysosomal enzyme galactocerebrosidase (GALC). Most patients confirmed to have Krabbe disease present before 6 months of age and die before 2 years of age. Older patients including adults with a slower clinical course are also identified. All patients have defects in myelination in both their peripheral and central nervous systems leading to significant neurologic features. The only treatment for pre-symptomatic infantile patients and mild later-onset patients is hematopoietic stem cell transplantation (HSCT). This treatment is less than ideal with most patients eventually developing problems with gait and expressive language within a few years of treatment. Several naturally occurring animal models are available, including twitcher (twi) mice, which have been used for many treatment trials. Initially, bone marrow transplantation (BMT) in young twi mice was shown to extend their lives from about 40 days to about 80 days. Later studies demonstrated that multiple injections of AAV vectors into the CNS of neonatal twi mice resulted in significant improvements. Additional improvement in lifespan were seen when the mice also received a bone marrow transplant together with gene therapy. Recently we showed that a single iv injection of AAVrh10-GALC on post-natal day (PND) 10 resulted in normal GALC activity in the CNS and high activity in the PNS with some extension of life and myelination. However, when twi mice received a single iv injection of AAVrh10-GALC one day after BMT on PND10 there was a great synergist effect. The mice show greatly extended lifespan (average survival of one year). Some mice lived two years. The treated mice exhibited normal behavior with improved myelination in both the CNS and PNS. Since HSCT is the standard of care in human patients although the outcomes are not ideal, adding this single iv injection of AAVrh10-GALC may greatly improve the treatment outcome.

MANNOSE-PHOSPHORYLATION IN HEALTH AND DISEASE

Thomas Braulke
University Medical Center Hamburg-Eppendorf, Children's Hospital, Dept. Biochemistry Hamburg, Germany

Mucolipidosis (ML) II and III are rare inherited disorders caused by mutations in the a/b subunits and g-subunits of the GlcNAc-1-phosphotransferase complex, respectively, encoded by the GNPTAB and GNPTG genes. These mutations either lead to total or partial loss of phosphotransferase activity that is required for modifications of lysosomal enzymes with mannose 6-phosphate (M6P) targeting signals. Therefore, MLII and III are biochemically related and characterized by missorting and hypersecretion of multiple lysosomal enzymes, lysosomal dysfunction and accumulation of non-degraded material, but exhibit different clinical courses of disease.

We have generated a novel knock-in mouse model of MLII by deletion of exons 14-16 in Gnptab (p.E885-1062del), and a Gnptg knock-out model of MLIII which mimic several clinical and biochemical symptoms of the human diseases. The analyses of these mice allowed us to gain further insight into pathomechanisms of early or late onset alterations in affected organs in MLII and MLIII.

Gnptg^{LacZ} reporter mice and RT-PCR revealed the expression of g-subunits mainly in the CNS, peripheral nervous system, skeleton, lung, kidney and fat tissues. In fibroblasts from *Gnptg*^{KO} mice the GlcNAc-1-phosphotransferase activity is reduced impairing M6P formation and sorting of distinct lysosomal enzymes. SILAC-based lysosomal proteome analysis and western blots revealed decreased amounts of 10 and 18 lysosomal enzymes (<20% and 20-50% of normal, respectively) in *Gnptg*^{KO} fibroblasts involved in the degradation of lipids, glycans and proteins. Similarly, the targeting of these lysosomal enzymes and the M6P formation are affected in primary *Gnptg*^{KO} osteoclasts and osteoblasts leading to accumulation of lysosomal storage material in bone and cartilage cells of *Gnptg*^{KO} mice. The data suggest that proper M6P formation on few lysosomal enzymes is essential for bone development and bone remodeling.

NOV 2, 2017
Scientific Program
3.00 p.m

ACTIVITY BASE PROFILING IN LIVE ZEBRAFISH REVEALS TGFSS REGULATION OF CATHEPSIN ACTIVATION DURING MLII PATHOGENESIS

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Cysteine cathepsins are known to play roles during development and disease that extend beyond their function in lysosomal protein turnover. The ability to temporally and spatially track cathepsin activity in live animals using activity-based probes provides an ideal opportunity to correlate proteolytic capacity with both normal cellular processes and the pathogenesis of disease specific phenotypes. Here we leverage a fluorescent activity-based probe (ABP), BMV109, to track cysteine cathepsins during development in normal and disease zebrafish embryos. Using this probe in a zebrafish model for mucolipidosis II, we demonstrate that loss of carbohydrate-dependent lysosomal sorting alters the activity of several cathepsin proteases and uncover for the first time a pathogenic mechanism whereby increased TGFß signaling sustains cathepsin K activation in developing cartilage. Our data supports a model in which TGFß signals enhance the proteolytic processing of pro-Ctsk by modulating the expression of chondroitin 4-sulfate, a mediator of Ctsk activation. We show elevated levels of chondroitin 4-sulfate in MLII embryos that correspond with increased TGFß-mediated expression of chst11, the primary sulfotransferase responsible for C4-S synthesis. Reducing the expression of chst11 in zebrafish impairs the proteolytic activation of cathepsin K and alleviates the MLII phenotypes caused by excessive activity of this protease. These findings uncover a new regulatory loop between TGFß signaling and Ctsk activation that is altered in the context of lysosomal disease. This work not only highlights the power of activity-based probes to identify mechanisms underlying pathogenic development in living animals, but it also suggests that disease associated changes in glycosaminoglycan profiles can profoundly alter the local activity cysteine proteases.

NOV 2, 2017
Scientific Program
3.50 p.m

FUNCTIONAL ANALYSIS OF GNPTAB AND GNPTG NULL CELLS IDENTIFIES REACTIVE OXYGEN SPECIES (ROS)-DEPENDENT INCREASES IN C-MET ACTIVITY

Megan Aarnio-Peterson, Peng Zhao, Seok-Ho Yu, Heather Flanagan-Steet, Lance Wells, Richard Steet

Acid hydrolases utilize a carbohydrate-dependent mechanism for lysosomal targeting. These hydrolases acquire a mannose 6-phosphate tag by the action of the GlcNAc-1-phosphotransferase enzyme, allowing them to bind receptors and traffic to endosomes. Loss of GlcNAc-1-phosphotransferase results in hydrolase hypersecretion and profound lysosomal storage. Little, however, is known about how these cellular phenotypes affect the trafficking and localization of surface glycoproteins. To address this question, we profiled the abundance of surface glycoproteins in WT and CRISPR-mediated GNPTAB-/- HeLa cells and identified changes in numerous glycoproteins, including altered abundance of multiple receptor tyrosine kinases. GNPTAB-/- cells also displayed elevated activation of several kinases including Met receptor. We found increased Met phosphorylation within both the kinase and docking domains, altered expression of Met-responsive genes and partial localization of the phosphorylated receptor to lysosomes in GNPTAB-/- cells. Partial increases in Met phosphorylation were noted in the GNPTG-/- cells, suggesting this effect was dependent on the degree of hydrolase mistargeting and/or lysosomal storage. Deactivation of Met signaling is regulated by receptor and non-receptor tyrosine phosphatases such as PTPRJ and PTP1B. Lower concentrations of pervanadate were needed to cause an increase in phospho-Met in GNPTAB-/- cells, suggesting decreased global phosphatase activity. GNPTAB-/- cells exhibited elevated levels of reactive oxygen species, known to inactivate phosphatases by oxidation of active site cysteine residues. Consistent with this mechanism, peroxide treatment of parental HeLa cells elevated phospho-Met levels while antioxidant treatment of GNPTAB-/- cells reduced phospho-Met levels. Collectively, these data identify new mechanisms whereby impaired lysosomal targeting can impact the activity of key growth factor receptors.

NOV 2, 2017
Scientific Program
4.10 p.m

ZEBRAFISH MODELS OF LYSOSOMAL DISORDERS ASSOCIATED WITH SKELETAL DEFECTS: CHALLENGING AN OLD PARADIGM OF DISEASE PATHOGENESIS

Stefania Bellesso[1], Roberto Costa[2], Marika Salvalaio[3], Rosella Tomanin[3], Susanna Lualdi[4], Mirella Filocamo[4] and Enrico Moro[1]

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In the past decades a growing attention has been paid to the understanding of biological aspects affected in lysosomal storage diseases (LSDs), beyond the traditional concept of substrate storage. To better elucidate primary mechanisms involved in the lysosomal functional impairment, several murine models have been generated so far. However, some of them exhibited evident limitations, including low viability and partial recapitulation of disease symptoms. To overcome these issues, in the last few years our group has been committed to generate and characterize fish models for type II Mucopolyshaccharidosis (MPSII, OMIM #309900) and type I Gaucher disease (OMIM#230800). By combining alternative approaches, we have been able to dissect early molecular defects occurring during a "pre-symptomatic stage", when lysosomal substrate storage is negligible. We, indeed, found that in both disorders the precocious failure of lysosomal function affects bone cell differentiation and homeostasis, as a consequence of well-defined cell signaling pathways alterations. Our results, therefore, challenge the current paradigm of LSDs pathogenesis limitedly based on the substrate storage, while we envisage the potential targeting of cell signaling cascades, as alternative complementary therapeutic strategy.

NOV 2, 2017
Scientific Program
4.30 p.m

A NATURAL HISTORY STUDY AND AAV-MEDIATED GENE THERAPY APPROACH FOR FELINE MUCOLIPIDOSIS II

Allison Bradbury

A naturally occurring feline model of mucolipidosis II (ML II) results from a nonsense mutation in the gene GNPTAB that is orthologous to disease-causing mutations in children. As in humans, the disease in cats is inherited as an autosomal recessive trait. Furthermore, feline ML II has a similar biochemical defect as humans, which leads to inclusion bodies and increased serum activities of numerous lysosomal enzymes including ą-mannosidase, ß-glucuronidase, and ą-fucosidase. The clinical signs in ML II cats closely recapitulate what is seen in human patients including skeletal, visual, and cardiac abnormalities.

Recent data in a mouse model demonstrated substantial CNS dysfunction associated with ML II. ML II mice exhibited progressive behavioral and sensorimotor impairment on a battery of tests. Brain pathology included dystrophic axons and neurites, loss of Purkinje cells, activation of astrocytes and microglia, and lysosomal distention. Seven ML II cats were evaluated as part of a natural history study with a focus on CNS and PNS abnormalities. Survival of ML II cats was 20.7 $\pm$ 2.6 weeks. ML II cats had impairments in hearing, as measured by brainstem auditory evoked response testing, and sensory nerve conduction, as measured by nerve conduction velocity testing. Interestingly, ML II cats demonstrated hydrocephalus and brain atrophy when evaluated by magnetic resonance imaging (MRI). Histologically, loss of Purkinje cells and neuroinflammation were not apparent in the brains of ML II cats, as seen in MLII mice. However, ML II cats did show increased expression of lysosomal associated membrane protein (LAMP) in much of the brain. The quantification of 19 different cytokines and chemokines was conducted in serum and cerebrospinal fluid (CSF) of ML II cats at 3 different time points (6, 12, and 18 weeks of age) and 3 were found to be dysregulated in the serum and 2 in the CSF.

Systemic delivery of adeno-associated virus serotype 9 (AAV9) gene therapy has shown great promise in animal models of multiple lysosomal storage disorders including neuronal ceroid lipofuscinosis, Tay-Sachs disease, Sandhoff disease, mucopolysaccharidosis (MPS) IIIA, MPS IIIB, MPS VII, and GM1 gangliosidosis. Additionally, intravenous delivery of AAV9 is currently being used in FDA approved human clinical trials for spinal muscular atrophy (NCT02122952) and MPS IIIA (NCT02716246), demonstrating true translation of this approach. In order to test this approach in the highly translatable feline model of ML II, an AAV vector expressing the wild type feline GNPTAB gene was generated and will be delivered intravenously to 1-week-old ML II cats. Since AAV9 has the propensity to cross the blood brain barrier, intravenous delivery will target the known ML II-related skeletal and connective tissue disease components as well as cardiac, retinal, and central nervous system (CNS) disease in a minimally invasive manner. Clinical disease progression in AAV-treated cats will be monitored by radiographs, echocardiograms, ophthalmologic exams, and MRI. Post mortem, tissues will be evaluated for restoration of enzyme activity, normalization of pathology, and biodistribution of the AAV vector.

NOV 2, 2017
Scientific Program
5.00 p.m

COATOMER PARTICIPATES IN THE GOLGI LOCALIZATION OF GLCNAC-1-PHOSPHOTRANSFERASE

Lin Liu, Balraj Doray, Stuart Kornfeld
Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110, USA

The Golgi enzyme – UDP-GlcNAc:lysosomal enzyme N-acetylglucosamine-1-phosphotransferase (phosphotransferase) mediates the first step in the generation of the mannose 6-phosphate sorting signal which directs newly synthesized lysosomal enzymes to lysosomes. Abnormal function of phosphotransferase is associated with the lysosomal storage diseases mucolipidosis II & III (ML II & ML III ą/ß). Previously, we reported that two ML III ą/ß missense mutations (K4Q, S15Y) in the phosphotransferase ą/ß N-terminal cytoplasmic tail (1-18aa) resulted in mislocalization to the endosome/lysosome system [1, 2]. Similar results were obtained with a new ML III patient mutation (R8G). We hypothesized that these mutations impaired binding of a cytoplasmic partner required for maintaining phosphotransferase in the Golgi. To identify the binding partner, we used the BioID method to detect proteins that interact with the wild-type but not the mutant N-terminal peptide. The BioID method is based on proximity-dependent cellular biotinylation by a bacterial biotin ligase that is fused to a bait protein to generate biotin labeled candidates in cells. The candidates are isolated by streptavidin beads and identified by liquid chromatography mass spectrometry (MS) analysis. We fused the biotin ligase to the C-terminal peptide of the wild-type and mutant phosphotransferase, and found several candidates (ARFGAP2, GOLGA5 and coatomer subunits) which are involved in retrograde protein trafficking from the trans-Golgi to the cis-Golgi or ER that interact with the wild-type peptide to a greater extent than with the mutant peptides. Next, we synthesized biotin labelled N-terminal wild-type peptide and peptides with K4Q, R8G or S15Y mutations, and confirmed that coatomer subunit COPD binds directly to the wild-type peptide but less so to peptides with K4Q, R8G or S15Ymutations. We conclude that coatomer maintains the Golgi localization of phosphotransferase by interaction with its N-terminal peptide and that loss of coatomer binding due to patient mutation leads to mislocalization of the mutant phosphotranferase to the endosome/lysosome system.

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NOV 2, 2017
Scientific Program
5:20 p.m

HEAT SHOCK PROTEIN-BASED THERAPIES AS CLINICAL CANDIDATES FOR SPHINGOLIPIDOSES

Thomas Kirkegaard Jensen*

Lysosomal storage diseases (LSDs) often manifest with severe systemic and central nervous system (CNS) symptoms. The existing treatment options are sparse and none of them are effective against the devastating neurological manifestations. We have demonstrated proof-of-concept for heat shock protein (HSP)-based strategies as potential pan-LSD therapies (1, 2). HSP70 improves the binding of several sphingolipid-degrading enzymes to their essential co-factor, bis(monoacylglycero) phosphate, in vitro and reverts lysosomal pathology in primary fibroblasts from patients suffering from a wide array of sphingolipidoses. It penetrates effectively to murine tissues including CNS, inhibits glycosphingolipid accumulation in murine models of Fabry (GLA-/-), Sandhoff (HEXB-/-) and Niemann-Pick type C (NPC1-/-) diseases, and effectively alleviates a wide spectrum a disease-associated neurological symptoms in HEXB-/- and NPC1-/- mice. Importantly, we have also demonstrated proof of concept for the small molecule HSP amplifier arimoclomol, which is currently being tested in a phase II/III clinical trial in Niemann-Pick type C (clinicaltrials.gov: NCT 02612129).

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NOV 3, 2017
Scientific Program
8.30 a.m

SIALIDOSIS (ML1) AND GALACTOSIALIDOSIS HISTORICAL AND CLINICAL OVERVIEW

Generoso Andria
Professor Emeritus of Pediatrics, Federico II University, Naples, Italy

A correct classification of a group of genetic metabolic diseases was in the past complicated by the fact that patients were categorized on the basis of clinical-pathological manifestations and metabolic-enzymatic abnormalities, when available. The molecular and genetic nature of the disease(s) was often clarified at a later stage, leading to a different classification. An example of such a confusion over time has been the nosology of inherited diseases associated with ß-galactosidase (ß-GAL) and/or neuraminidase (NEU) deficiency. The best case of nosological "lumping and splitting" is offered by Galactosialidosis (GS), a glycoproteinosis characterized by a combined deficiency of ß-GAL and NEU1, which is secondary to a primary defect of the serine carboxypeptidase/protective protein cathepsin A (PPCA). In the seventies some of the patients with GS were described as atypical variants of GM1 gangliosidosis on the basis of low levels of ß-GAL activity. In 1975, complementation studies after somatic cell hybridization in some of them indicated the involvement of a different gene. In 1977 a profound deficiency of NEU was described by few groups in an infantile Hurleroid disorder, already known as Mucolipidosis I, and in adult patients with macular cherry-red spots and myoclonus without dementia. A year later Wenger's group found a NEU deficiency in cells from a girl with ß-GAL deficiency, already classified as a variant form of GM1 gangliosidosis. The combined deficiency of both enzymes was then confirmed in other similar subjects. These observations prompted Lowden and O'Brien, in 1979, to propose a classification of "primary" neuraminidase deficiency, called Sialidosis, that included, in the Type 2-Dysmorphic Group, both patients with coexistent deficiency of NEU and ß-GAL and patients with isolated NEU deficiency. Soon these two groups of patients were shown to be genetically heterogeneous by complementation analysis after somatic cell hybridization. On these bases in 1981 we proposed to name "Galactosialidosis" the disorder with a combined deficiency of ß-GAL and NEU, and restrict the term "Sialidosis" to the isolated NEU defects. The discovery of the PPCA as the primary defect of GS by d'Azzo et al. in 1982 definitely solved the nosological issue and the subsequent work of her group over the years is now eventually leading to innovative therapeutic approaches for this disease.

Acknowledgements: I would like to thank Alessandra d'Azzo, Hans Galjaard and William S. Sly for what I learned from them in many years of collaboration and friendship.

NOV 3, 2017
Scientific Program
9.00 a.m

MOLECULAR PATHOPHYSIOLOGY IN SIALIDOSIS: LINKS TO ADULT CONDITIONS OF AGING

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Sialidosis (mucolipidosis I) and galactosialidosis are neurodegenerative, glycoprotein storage diseases associated with primary or secondary deficiency of the lysosomal sialidase NEU1. This enzyme regulates the catabolism of sialo-glycoconjugates by removing their terminal sialic acids. The complex phenotypes characteristic of both diseases predict a spectrum of deregulated pathways downstream of NEU1 deficiency and accumulation of over-sialylated substrates, which are likely cell-and tissue-specific. Here, I will summarize recent advances in the study of sialidosis. Using Neu1−/− mice, a preclinical model of the disease, we have unraveled mechanisms of pathogenesis that have broadened our understanding of the physiological roles of NEU1. One such process is calcium-dependent lysosomal exocytosis, which is negatively regulated by NEU1. NEU1 restrains lysosomal exocytosis by cleaving the sialic acids on LAMP1. This influences the protein's turnover rate and, in turn, limits the number of exotic lysosomes docking at and fusing with the PM. In absence of NEU1, oversialylated LAMP1 accumulates at the lysosomal membrane, which results in excessive exocytosis of soluble hydrolases and exosomes into the extracellular space. Ultimately, unrestrained lysosomal exocytosis impacts on cell adhesion, cell-cell communication, PM composition and ECM integrity. We demonstrated that exacerbated lysosomal exocytosis is at the basis of disease pathogenesis in Neu1−/− mice, but its pathological effects on cell and ECM homeostasis can be applied to other adult diseases of unknown etiology, like non-familial Alzheimer's disease and idiopathic pulmonary fibrosis. We are developing state-of-the-art cellular models to better define the potential implications of these findings for clinical care and therapy of sialidosis and potentially of more common adult conditions of aging.

(This study was supported in part by NIH grant GM060950, DK095169, the Assisi Foundation of Memphis, Ultragenyx Pharmaceuticals, and ALSAC of St. Jude Children's Research Hospital).

NOV 3, 2017
Scientific Program
9.30 a.m

LYMPHATIC PATHWAY IN GLYCOPROTEINOSES

Noelia Escobedo[1], Yvan Campos[2], Elida Gomero[2], Jieun Kim[2], Randall Wakefield[2], Linda Horner[2], Alessandra d'Azzo[2]

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Meningeal lymphatics are a recently discovered network of lymphatic vessels, running parallel to the dural sinuses and meningeal arteries of the mammalian central nervous system (CNS). The meningeal lymphatics drain excess fluid from the CNS, and filter immune cells and small molecules into the deep cervical lymph nodes. Currently, the role that this system plays in neurodegenerative lysosomal storage diseases is yet to be explored. Neuraminidase 1 (NEU1) is a lysosomal sialidase essential for initiating the degradation of glycoproteins containing the sugar sialic acid at the end of their glycan chains. This process is important for lysosomal catabolism and maintenance of cell and tissue homeostasis. NEU1 deficiency causes the lysosomal storage disease sialidosis. The $NEU1^{-/-}$ mouse model of sialidosis develops severe neurologic abnormalities, characterized by progressive build-up of Aß-amyloid deposits; hence, it represents a spontaneously occurring model of Alzheimer's disease (AD). Considering that protein aggregates are most likely to be removed from the cerebrospinal fluid (CSF) via the meningeal lymphatic vessels into the periphery, we wanted to investigate the characteristics of the lymphatic vasculature in the context of NEU1 deficiency. Our results show that $NEU1^{-/-}$ mice have much more lymphatic vessels with more ectopic branches; in some areas, the vessels look highly dilated with ruptured cell membranes and abnormal protrusions. Scanning electron microscopy of the meninges showed extensive vacuolation in endothelial cells of the lymphatic vessels and the tissue around. Sequential Magnetic Resonance Imaging (MRI) scans of crania in Neu1 mouse showed that the phenotype is also accompanied by accumulation of the CSF in the brain and olfactory bulb. These results imply a severe defect in the lymphatic vasculature caused by NEU1 deficiency that may contribute to the CNS pathogensis.

NOV 3, 2017
Scientific Program
10.00 a.m

FACTORS REGULATING TRANSCRIPTION OF THE LYSOSOMAL SIALIDASE NEU1

Ida Annunziata (Alessandra d'Azzo Laboratory)
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NEU1 is a lysosomal exo-glycosidase that catalyzes the cleavage of terminal N-acetylated neuraminic acids (sialic acid) linked to the saccharide chains of glycoproteins, glycolipids as well as oligo- and polysaccharides. Deficiency of NEU1 is at the basis of sialidosis, a rare neurosomatic lysosomal storage disease. No cure is currently available for sialidosis. The $Neu1^{-/-}$ mice, a faithful mouse model of the disease, develop a neurodegenerative condition resembling Alzheimer's disease (AD). We demonstrated that the progressive formation of ß-amyloid deposits in the hippocampus, was the direct consequence of two events occurring synergistically: 1) accumulation and lysosomal processing of an oversialylated APP, a novel substrate of Neu1; 2) increased lysosomal exocytosis by neural cells of toxic Aß-42 peptide into the brain CSF and interstitial fluid. We also found that by crossing a transgenic mouse model of AD into the *Neu1*$^{-/-}$ genetic background we could accelerate ß-amyloid deposition and plaque formation. Conversely, the upregulation of Neu1 in these AD mice by an AAV-mediated gene therapy approach strikingly ameliorates both phenotypes (Annunziata et al., Nature Commun 2013). Thus, the sialidosis mice represent a spontaneously occurring model of AD, suggesting that NEU1 deficiency/downregulation is a risk factor for the development of the disease.
We have built upon this data and tested this hypothesis in a cohort of brain specimens and CSF samples obtained from AD patients. Our initial results point to a selective downregulation of NEU1 in AD samples which is accompanied by increased lysosomal exocytosis in their CSF. As logic follow up, we started to look at the mode of regulation of NEU1 transcription and found that the gene is epigenetically regulated. This study may have important implications and offer potential therapeutic targets for 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)]

NOV 3, 2017
Scientific Program
10.20 a.m

ENZYME REPLACEMENT THERAPY FOR GALACTOSIALIDOSIS, TOWARDS THE CLINICAL TRIAL

Vish Koppaka[a], Jaclyn Cadaoas[a], Sean Cullen[a], Creobelle Guzman[a], Christine Haller[a], Huimin Hu[b], Kartika Jayashankar[a], Mike Machado[a], Gabrielle Boyle[a], Rosario Mosca[b], Arjun Natesan[a], Andrea Schatz[a], Michael Vellard[a], Alessandra d'Azzo[b]

[a]**Ultragenyx Pharmaceutical, Novato, CA, United States**
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Galactosialidosis (GS) is a lysosomal storage disease caused by a primary deficiency of the serine carboxypeptidase Protective Protein/ Cathepsin A (PPCA). This affects the activity and stability of Neuraminidase 1 (NEU1) and ß-galactosidase (ß-GAL), leading to the progressive accumulation of sialylglycoconjugates in tissues and body fluids of GS patients. There is currently no approved drug for the treatment of GS.

We are investigating a recombinant human PPCA (rhPPCA) as a potential therapeutic for the treatment of GS patients. Administration of rhPPCA in GS patients is predicted to restore NEU1 and ß-GAL activities and reduce the buildup of over-sialylated substrates in tissues and body fluids.

We have developed a mammalian cell line that over expresses rhPPCA, and a reliable process for purification of the recombinant protein. Preliminary in vitro experiments have demonstrated uptake and delivery to the lysosome via the mannose-6-phosphate receptor pathway, followed by rescue of NEU1 and ß-GAL activities.

A proof-of-concept study was performed in the GS mouse model to determine the therapeutic efficacy of rhPPCA by intravenous administration. Following treatment, a dose-dependent increase in cathepsin A activity was detected in multiple affected organs including liver, kidney, heart, spleen and brain. This was accompanied by a rescue of NEU1 activity, normalization of ß-GAL levels, diminished cytoplasmic vacuolation and a reduction of urinary sialyloligosaccharides. This study demonstrated clear dose-dependent efficacy and no toxicity.

The next steps are to conduct IND-enabling pharmacology/toxicology studies and to identify patients globally for a clinical trial. We have initiated a no-cost testing program for potential patients with GS. Interviews with physicians and patients are being conducted to gain insight into the GS patient experience, and develop clinically meaningful endpoints.

NOV 3, 2017
Scientific Program
11.00 a.m

MYOCLONUS IS A KEY SYMPTOM OF THE ADULT FORM OF SIALIDOSIS TYPE I

Laura Canafoglia[1], Simona Allievi[2], Cinzia Gellera[2] and Silvana Franceschetti[1]

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[1] Dept of Neurophysiopathology
[2] Dept of Biochemistry and Genetics

Sialidosis Type I has a juvenile or adult onset, presenting with rare generalized seizures, myoclonus, ataxia, and cherry red spot and it typically lacks mental deterioration or dysmorphisms. Electrophysiological studies on patients with sialidosis demonstrated the cortical origin of the myoclonus, detecting a consistent temporal relationship between EEG spikes or central fast activity and spontaneous or action activated myoclonic jerks, similarly with that observed in other forms of progressive myoclonus epilepsies (PME). However, a strong rhythmicity of the myoclonus associated with a high corticomuscular coherence is a consistent finding in sialidosis but less common of other PME forms. This pattern of myoclonus probably justifies the especially severe motor impairment in sialidoses. In some patients with adult onset, myoclonus represents the unique relevant symptom, unless seizures neither macular cherry-red spot and its detection and classification is necessary to recognize the disease, while additional signs including cataract, femoral head necrosis, scoliosis, syringomyelia, and multiple vertebral deformities may strengthen the diagnostic hypothesis. In the patients' management, two main issues are of great importance: the first is the definition of a clinical and electrophysiological protocol for quantification of the movement disorder and of the other symptoms. The second issue is the optimization of a symptomatic treatment for myoclonus. Besides the research of drugs or procedures targeted to act on the etiological mechanisms, there is the need of testing drugs for reducing the symptoms and ameliorating the quality of life. Selection of the best available therapy needs studies using standardized procedures capable of comparing patients' conditions in the pre- and post-treatment phases, possibly involving several centres to increase the number of observations.

NOV 3, 2017
Scientific Program
11:20 a.m

MOLECULAR DIAGNOSIS OF GLYCOPROTEINOSES

Amelia Morrone

The glycoproteinoses are rare inherited lysosomal storage diseases (LSDs) caused by genetic alterations that lead to total or partial deficiency of enzymatic and non-enzymatic lysosomal proteins. Biochemical tests are important tools for diagnosing these rare diseases. However, molecular genetic analysis remains essential for confirming or excluding a pathology and to identify pathogenic variants in candidate genes on a biochemical basis.

The detection of disease-causing variants in a proband, besides providing diagnostic confirmation, allows accurate genetic counselling as well as the possibility of identifying at-risk family members and offering molecular prenatal diagnostic testing.

At present, molecular genetic testing involves DNA sequencing using the Sanger method or employing Next Generation Sequencing (NGS) platforms. This presentation will address and discuss the pros and cons of the biochemical and molecular diagnosis of the glycoproteinoses using the NGS and Sanger approaches.

The importance and difficulties of functional studies, needed to clarify the role of novel genetic variants of unknown significance that are frequently identified in LSDs, will also be underlined.

We will present our experience in this field and the difficulties of in vitro experiments in challenging cases that require timeframes that can be incompatible with the clinical needs of a rapid response. Bioinformatics software, which uses tools to consider the phylogenetic conservation of amino acid residues, or identify mutational consequences by means of splicing defect prediction algorithms and homology modelling, or which provide assistance in predicting the pathogenetic role of new variants, will also be discussed. The results of these investigations, though predictive and non-definitive, are still important in determining whether a variant is likely to be pathogenic and in indicating whether in vitro functional studies should be carried out.

In the diagnosis of glycoproteinoses, beside the importance of molecular genetic confirmation, multidisciplinary collaboration between laboratory and clinical specialists remains essential.

NOV 3, 2017
Scientific Program
11.30 a.m

EPILEPSY IN LYSOSOMAL STORAGE DISEASES

Renzo Guerrini MD, FRCP

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Different lysosomal storage diseases are complicated by different types of epilepsy. In some disorders, the clinical presentations and accompanying neurophysiological features become over time characteristic of a severe progressive condition, in the context of a syndrome of generalised neurological deterioration. In other forms, epilepsy may have nonspecific features or remain a marginal clinical manifestation whose characteristics and severity do not necessarily suggest, per se, a progressive condition until the overall clinical picture deteriorates.

Epileptic seizures are commonly reported in individuals with mucopolysaccharidoses type II and III. In Mucopolysaccharidosis type II (or Hunter syndrome), which is an X-linked disorder, epilepsy is observed in up to one third of patients with an age at onset of about 10 years and represents an early clinical manifestation of brain involvement, especially in the more severe forms of the disease. Generalized seizure types including absence, myoclonic, and generalised tonic-clonic are common. In mucopolysaccharidosis type III, epilepsy usually follows in about two thirds of the patients the onset of cognitive deterioration and behavioural disorders, appearing at around age 11 years, although age at onset may vary widely. Patients with severe MPS IIIA develop epilepsy with respect to those with the less severe forms of the disease.

In the wide category of the Sphingolipidoses epileptic seizures are particularly common in Farber, GM1 Gangliosidosis type II, GM2 Gangliosidosis, Gaucher type III, metachromatic leukodystrophy and Krabbe. The most typical clinical presentation is observed in Gaucher type III in which the phenotype is one of progressive myoclonus epilepsy with cortical reflex myoclonus, C-reflex and giant visual and somatosensory evoked potentials, whose characteristics need be differentiated from other disorders typical of the late childhood age such as Lafora disease and some mitochondrial disorders. A form of progressive myoclonus epilepsy, associated with generalised seizure types is also observed in patients with *ASAH1* gene mutations and a severe neonatal onset form of Farber disease in which early neurological deterioration with lethargy is associated with hydrops fetalis, hepato-splenomegaly, granulomatous infiltrations of the organs and muscle atrophy. In the GM1 Gangliosidoses, epilepsy is especially observed in the infantile type I and II forms. In type I, onset is characterized by early neurological deterioration, usually within the 6th month, visceromegaly, facial and skeletal abnormalities, cherry red spot, and generalized seizures. In Type II, which usually starts within the first 3 years of life, epilepsy is associated with progressive neurological manifestations, including strabismus, motor awkwardness, weakness, and lethargy. In the GM2 Gangliosidosis, which encompasses

disorders caused by three different genes (*HEXA*, *HEXB* and *GM2A* genes) include Tay-Sachs disease and Sandhoff disease which are complicated by severe epilepsy especially when manifested in the late infantile forms and in their advanced stages. Multiple seizure types, both focal and generalized, have been reported. In Krabbe disease, or globoid-cell leukodystrophy, severe generalised or focal seizures and infantile spasms have been described even in the early stages, while in Metachromatic leukodystrophy epileptic seizures tend to appear during the advanced stages.

The different disorders belonging to the category of the Oligosaccharidoses (Aspartylglucosaminuria, Fucosidosis, b-mannosidosis, and Schindler's disease) are complicated by epilepsy in less than one third of patients, exhibiting variable, mostly unspecific characteristics and with variable impact on the general conditions of patients. In Aspartylglucosaminuria for example, the prevalence of epilepsy increases with age, while in b-mannosidosis, whose clinical spectrum is quite variable, early, even neonatal onset seizure onset has been described.

Transmembrane Protein Defects, which include Infantile Free Sialic Acid Storage (ISSD) and Salla disease are both complicated by epilepsy in about one third of individuals. Seizures and epilepsy follow the expression of the disease, which has an early onset and very severe course in ISSD and a later onset and a less rapidly progressive course in Salla disease. In Niemann-Pick (Type C1) epileptic seizures appear usually late in the course, in the context of a syndrome of severe cognitive and generalised neurological deterioration with onset in late childhood. Some patients have nonspecific features while others exhibit a form of progressive myoclonus and epilepsy. Finally, epilepsy is also frequently seen in Austin's disease, due to mutations in the *SUMF1* gene. The variable ages at onset, from the neonatal period to adolescence imply variable manifestations of epilepsy, which is however dominated by severe generalised seizure types.

There is therefore a considerable variability within which the clinician should always address the diagnostic and therapeutic implications in the wider clinical context.

NOV 4, 2017
Scientific Program
8.30 a.m

INTRACEREBROVENTRICULAR CERLIPONASE ALFA FOR CHILDREN WITH CLN2 DISEASE: INTERIM RESULTS FROM AN ONGOING PHASE 2 EXTENSION STUDY

Angela Schulz[1], Nicola Specchio[2], Paul Gissen[3], Emily de los Reyes[4], Heather Cahan[5], Peter Slasor[5], Temitayo Ajayi[5], David Jacoby[5]

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[2] Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
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[4] Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA
[5] BioMarin Pharmaceutical Inc., Novato, CA, USA

BACKGROUND: CLN2 disease, a rare, inherited, pediatric, neurodegenerative lysosomal storage disorder caused by TPP1 deficiency, is characterized by seizures, ataxia, language and motor function loss, blindness and early death. A phase 1/2 study (NCT01907087) demonstrated that intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa, a recombinant human TPP1 enzyme, every other week for 48 weeks was associated with attenuation of CLN2 disease progression. This extension study (NCT02485899) assesses the long-term safety and efficacy of ICV-administered cerliponase alfa in children with CLN2 disease for up to 240 weeks.

DESIGN: Subjects who completed the phase 1/2 study enrolled in this open-label extension study, and continued receiving 300 mg cerliponase alfa qow. Cumulative data from both studies were used to evaluate long-term safety (assessed by analysis of adverse events (AEs)) and efficacy (assessed by changes in motor and language (ML) functions using the CLN2 clinical rating scale).

RESULTS: 24 subjects were initially treated with cerliponase alfa in the phase 1/2 study (9 male, 15 female, mean (SD) age 4.3 years (1.24)); 23 subjects enrolled in the extension study (74 to 124 weeks total exposure). All had AEs; most were Grade 1-2. Common AEs included pyrexia, hypersensitivity and convulsion. Nineteen (79%) subjects had at least one serious AE, which were mostly consistent with neurodegenerative disease in a pediatric population. Significant attenuation of the rate of decline in ML score (mean (95% CI): 0.32 (0.13, 0.52) points/ 48 weeks, p<0.0001) was observed compared with a rate of decline of 2.0 points/48 weeks in untreated patients. The responder (<2 point loss) rate at 81 weeks (87%, p = 0.0002) was unchanged compared to that observed at 48 weeks, suggesting a persistent treatment effect.

CONCLUSIONS: These data suggest that enzyme replacement therapy with ICV-administered cerliponase alfa has an acceptable safety profile and a sustained effect over time.

NOV 4, 2017
Scientific Program
9:00 a.m

PERSONALIZED THERAPY APPROACHES FOR AGU

Antje Banning, Leonie Voll, Annika Jurkat, Steven J. Gray, Juha Rouvinen, 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 can be as high as 50 years. Although AGU is more common in Finland, an increasing number of AGU cases have recently been diagnosed elsewhere in the world.

AGA is a heterotetrameric enzyme $(\alpha\beta)_2$ 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-major, 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 characterized the consequences of some newly-identified and known AGU missense mutations and show that some of these mutations, including AGUFin-major, cause a local mis-folding of AGA, which is sufficient to impair the processing into the active form. These mutant enzymes thus may retain their capacity to be activated and are localized in lysosomes. However, the correct folding of the mutant AGA can also be obtained by means of pharmacological chaperones that we have recently identified. We here also provide some potential personalized therapy options for patients exhibiting other mutations, including nonsense and splicing defects that are not susceptible to the chaperone therapy. Our data show that although ERT and gene therapy can be considered as universal, mutation independent therapy options, alternative, more individual and less invasive approaches may be suitable for patient groups with specific mutations.

NOV 4, 2017
Scientific Program
9.30 a.m

AAV9-BASED GENE THERAPY IN ASPARTYLGLUCOSAMINURIA MICE

Xin Chen[1], Sarah Snanoudj-Verber[1,4], Laura Pollard[2], Sara Cathey[2], and Steven J. Gray[1,3]

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[2]Greenwood Genetics Center, Greenwood, SC, USA
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Aspartylglucosaminuria (AGU) is an autosomal recessively inherited lysosomal storage disease. It is caused by the absence of functional lysosomal enzyme aspartylglucosaminidase (AGA), resulting in the accumulation of AGA substrate, aspartylglucosamine (GlcNAc-Asn) in different body fluids and tissues. In humans, AGU is a progressive disorder characterized by intellectual disability, skeletal abnormalities, and early mortality. Currently, there is no cure for AGU and patient care usually includes medical, social, and educational rehabilitation. Due to the failure of bone marrow transplantation and the lack of feasibility of enzyme replacement therapy in this disease, gene therapy becomes a key strategy which might provide a therapeutic benefit. Supporting this, previous adenovirus-mediated gene therapy was demonstrated to be effective in locally reducing lysosomal storage in the brain (intraparenchymal route) and fully correcting it in liver (IV route) of AGU mice. Over the past decade, adeno-associated virus (AAV) gene therapy has progressed rapidly and many groups have shown that AAV9 vectors can confer a dramatic therapeutic improvement to various neurological disorders. Therefore, we hypothesized that AAV9-based gene therapy may impart a therapeutic benefit to AGU mice. To test this hypothesis, a construct carrying the codon-optimized human AGA gene was packaged into AAV9 capsids as a self-complementary (sc) genome. The scAAV9/AGA vectors were then injected by tail vein into adult AGU mice at 2x1011 vg/mouse. Mouse serum and urine were collected to measure serum AGA activity and urine GlcNAc-Asn excretion, respectively, at one week before and multiple time points post injection. Our results clearly show that IV injection of scAAV9/AGA vectors dramatically increases serum AGA activity 1 week post injection to a super physiological level (treated KO vs KO vs Het mice: 736.4±46.9 vs 0 vs 10.0±1.3 nmol/24hr/ml serum). By 4 weeks post injection, serum AGA activity in about half of treated mice is sustained. In the other half, activity decreases to less than one third of that at 1 week post injection but is still significantly higher than in heterozygous mice. There is no further decrease of serum AGA activity in any of those treated mice between 4 to 32 weeks post injection. On the contrary, urine GlcNAc-Asn excretion decreases substantially in scAAV9/AGA vector treated groups at 4 (treated KO vs KO vs Het mice: 13±14 vs 1132±473 vs 0 mg GlcNAc-Asn/g creatinine) and 8 (treated KO vs KO vs Het mice: 14±14 vs 786±429 vs 0 mg GlcNAc-Asn/g creatinine) weeks post injection. Taken together, these results suggest that IV administration of scAAV9/AGA vectors can almost completely clear peripheral GlcNAc-Asn accumulation in AGU mice. More importantly, our preliminary data show that this treatment can also restore the impaired movement in AGU mice. Similar results have been achieved in mice dosed by lumbar intrathecal injection. More behavioral tests, small animal imaging, and histopathological staining are being used to determine if these treatment benefits extend to the central nervous system. The results from the study suggest that gene therapy could be considered for possible future human translation.

NOV 4, 2017
Scientific Program
10.00 a.m

A MOUSE MODEL FOR FUCOSIDOSIS

Heike Wolf[1], Lennart Korf[1], Markus Damme[2], Stijn Stroobants[3], Rudi D'Hooge[3], Hans Christian Beck[4], Renate Lüllmann-Rauch[6], Thomas Dierks[1] and Torben Lübke[1]*

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Fucosidosis is an ultra-rare autosomal recessive lysosomal storage disorder caused by the deficiency of the lysosomal ą-L-fucosidase. We generated a fucosidosis mouse model that completely lacks ą-L-fucosidase activity leading to highly elevated amounts of fucosylated glycoconjugates in all tissues and organs analyzed as well as in the urine[1]. Lysosomal storage pathology was observed in many visceral organs like liver, kidney, spleen and bladder as well as in the central nervous system (CNS). In the CNS, various cell types were affected by enlargement of the endo-lysosomal sytem, neuroinflammation and a progressive loss of Purkinje cells resulting in various behavioral deficits[1]. We have just begun to take advantage of our fucosidosis mouse model with regard to therapy approaches like conventional enzyme replacement therapy (ERT). However, due to the limited accessibility of the predominantly affected CNS by ERT, we are also considering alternative strategies like virus-based gene therapy or RTB lectin-mediated enzyme delivery[2].

1) Wolf H, Damme M, Stroobants S, D'Hooge R, Beck HC, Hermans-Borgmeyer I, Lüllmann-Rauch R, Dierks T, Lübke T (2016) A mouse model for fucosidosis recapitulates storage pathology and neurological features of the milder form of the human disease. Dis Model Mech. 9:1015

2) Acosta W, Ayala J, Dolan MC, Cramer CL (2017) RTB Lectin: a novel receptor-independent delivery system for lysosomal enzyme replacement therapies. Sci Rep. 18:14144

NOV 4, 2015
Scientific Program
10.30 a.m

A GALNAC TRANSFERASE/ASPARTYLGLUCOSAMINURIA DOUBLE KNOCKOUT MOUSE MODEL EXPERIENCES RAPIDLY ACCELERATED DISEASE OVER THE SINGLE ASPARTYLGLUCOSAMINURIA KNOCKOUT MODEL.

N. Matthew Ellinwood[1], Elizabeth M. Snella[1], Vincent Gugliemi [1], Charles J. Arends [1], Steven J. Gray[2], Tyler A. Harm[3], Jodi D. Smith[3], Bethann Valentine[1]

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[3] Iowa State University College of Veterinary Medicine, Department of Veterinary Pathology

The enzyme GalNAc transferase (GalNAcT) is necessary for production of complex gangliosides. A GalNAcT knockout murine model has been used to investigate complex gangliosides in both normal physiology and in experiments involving double knockout (DKO) mice and genetic substrate deprivation. We previously showed in the context of primary heparan sulfate lysosomal storage, that GalNAcT/MPS III DKO mice had rapid acceleration of disease. The DKO mice succumbed to overt ataxia and urine retention at roughly twice the speed of single MPS IIIA or MPS IIIB mice. We wished to determine if this interaction is specific to heparan sulfate storage, or if it is a generic effect of neuropathic lysosomal storage disease. Thus we explored the hypothesis that the GalNAcT DKO effect was specific to primary storage of heparan sulfate.

We produced DKO mice deficient in GalNAcT and affected with Aspartylglucosaminuria (AGU), a lysosomal storage disease model clinically similar to murine MPS III, but with a different primary substrate. Both models' phenotype involve an adult onset of clinical signs which include neurologically determined urine retention and humane endpoints being reached at 12-15 months of age. Preliminary findings have found that at the age of 12-16 weeks there is no clearly discernable grossly visible signs of disease in the AGU/GalNAcT DKO mice. At 30 weeks of age the GalNAcT/AGU mice show overt ataxia, poor pelage, and pronounced urine retention relative to their grossly unaffected single knockout littermates, reaching humane endpoints at a much earlier time point than previous reports (up to 18 months of age).

These findings indicated that elimination of complex gangliosides accelerates murine lysosomal disease in a non-substrate specific manner. Previous GalNAcT/MPS III DKO mice had severely impacted white matter. Further characterization of these two distinct DKO mice could aid in elucidating the neuropathological mechanism in associated lysosomal storage disease.

NOV 4, 2017
Scientific Program
12:10 p.m

THE GENETIC DIAGNOSIS: A LONG AND COMPLEX CASE OF MUCOLIPIDOSIS III IN BRAZIL

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INTRODUCTION: Mucolipidosis III alpha/beta (MIM #252600) is an autosomal recessive disease caused by absence or defect in the manose-6-phosphate markers responsible for the lysosomal hydrolases targeting to lysosomes. The deficient enzyme is N-acetylglucosamine-1-phosphotransferase, encoded by GNPTAB and GNPTG genes and formed by two α, β and γ subunits. The genetic diagnosis by Sanger is able to identify 90% of alterations.

PURPOSE: To describe the genetic investigation of a Brazilian patient with biochemical and clinical diagnosis of ML III whose genotype was not established by Sanger sequencing.

METHODOLOGY: DNA from a patient and his parents were extracted from peripheral blood with Easy-DNA purification kit (Thermo Fisher Scientific). DNA was amplified by PCR and GNPTAB and GNPTG genes were sequenced in an ABI-PRISM 3500 for Sanger method and in an Ion PGM Hi-Q sequencing kit by next generation sequencing (NGS). RNA of the patient was extracted with PAXgene blood RNA kit (Qiagen). cDNA was generated with High Capacity cDNA reverse transcription kit (Thermo Fisher Scientific).

RESULTS: The Sanger method identified the GNPTAB pathogenic mutation c.242G>T (exon 3) in heterozygosity in the patient and his father. Patient sample did not amplify exon 1, however samples for his parents amplified normally and the analysis indicated no alterations in this exon. NGS results were similar for GNPTAB and negative for alterations in GNPTG. The sequencing of patient cDNA by Sanger identified the r.86_116delins86+19_49 and r.242g>t in exon 1 and 3, respectively.

DISCUSSION/CONCLUSION: This work demonstrated Sanger and NGS limitations in detecting large insertions/deletions. For these reasons, RNA analysis may be important to conclude the genetic diagnosis and to perform the genetic counseling.

NOV 4, 2017
Scientific Program
12:30 p.m

Poster Abstracts

AAV9-BASED GENE THERAPY RESTORES AGA ENZYMATIC ACTIVITY IN A MOUSE MODEL FOR ASPARTYLGLUCOSAMINURIA

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Aspartylglucosaminuria (AGU) is an autosomal recessively inherited lysosomal storage disease. It is caused by the absence of functional lysosomal enzyme aspartylglucosaminidase (AGA), resulting in the accumulation of AGA substrate, aspartylglucosamine (GlcNAc-Asn) in different body fluids and tissues. AGU is a progressive disorder characterized by intellectual disability, skeletal abnormalities, and early mortality. Currently, there is no cure for AGU. Previous adenovirus-mediated gene therapy was demonstrated to be effective in locally reducing lysosomal storage in the brain (intraparenchymal route) and fully correcting it in liver (intravenous route) of AGU mice. Over the past decade, adeno-associated virus (AAV) gene therapy has progressed rapidly and AAV9 vectors have been shown to confer a dramatic therapeutic improvement to neurological disorders. Therefore, we hypothesized that AAV9-based gene therapy may impart a translationally-relevant therapeutic benefit to AGU mice. A construct carrying the codon-optimized human AGA gene was packaged into AAV9 capsids as a self-complementary (sc) genome. The scAAV9/AGA vectors were injected by tail vein into adult AGU mice at 2x10 11 vg/mouse. Our results show that IV injection of scAAV9/AGA vectors dramatically increases AGA activity to a super physiological level, sustained at least 32 weeks post injection. The treatment is also capable of completely normalizing the urine GlcNAc-Asn at 4 and 8 weeks post injection. These results suggest that IV administration of scAAV9/AGA vectors can almost completely clear peripheral GlcNAc-Asn accumulation in AGU mice. Similar results have been achieved in mice dosed by lumbar intrathecal (IT) injection. In one pilot mouse examined following an IT dose of 1x10 11 vg, AGA activity was restored to normal levels in both the brain and the liver. Behavioral tests, neuroimaging, and histopathological staining are under way to determine the full extent of therapeutic benefit. The results from the study suggest that gene therapy could be considered for possible future human translation.

NONPATHOGENIC VARIANTS OF THE GNPTAB GENE - A SOUTHERN BRAZIL HEALTHY POPULATION ANALYSIS

Malu Bettio Soares[1], Fernanda Sperb-Ludwig[1,3], Ida Vanessa Doederlein Schwartz[1,2,3]

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[2] Hospital de Clínicas de Porto Alegre, Department of Genetics and Postgraduate Program in Genetics and Molecular Biology

The GNPTAB gene is located at chromosome 12q23.3, contains 21 exons, and encodes two (alpha and beta) subunits of N-acteylglucosamine- 1-phosphotransferase. This enzyme has a key role in the synthesis of Mannose-6- phosphate (M6P) which assists in the correct addressing of lysosomal hydrolases to lysosome. Pathogenic alterations in this gene result in Mucolipidosis (ML) II or III alpha/beta, while some nonpathogenic variations are associated with stuttering. The objective of this study was to determine the frequency of nonpathogenic variants of the GNPTAB gene in Southern Brazil's healthy population.

One hundred peripheral blood samples of non-related blood donors from Porto Alegre (South Brazil) were collected, DNA was extracted (Easy-DNA kit – Invitrogen), and sequenced through the Sanger method. Seven variants previously found in Brazilian ML II/III patients were analyzed: c.323+20delT; c.365+96_97delGT (rs 4015837); c.365+145C>T (rs 2108694); c.1285-166G>A (rs 7963747); c.1932A>G (rs 10778148); c.3135+5T>C (rs 759935); and c.3336-25T>C (rs 3736476).

The frequencies observed were: c.323+20delT (0%), c.365+96_97delGT (41.5%), c.365+145C>T (46%), c.1285-166G>A (64%), c. 1932A>G (65%), c.3135+57T>C (58%), c.3336-25T>C (45.5%). GNPTAB is a highly polymorphic gene. The highest frequency was found for the c.1932A>G variant, similar only to the one found in the African population, a finding that can be explained by the colonization of Brazil. The data generated by this study will be useful for future haplotypic analysis.

EXOSOME-DRIVEN EMT PROMOTES FIBROSIS AND MUSCLE DEGENERATION IN THE MOUSE MODEL OF THE LYSOSOMAL DISEASE SIALIDOSIS

Diantha van de Vlekkert[1], Huimin Hu[1], Elida Gomero[1], Xihn-Xihn Nguyen[2], Carol Feghali-Bostwick[2], Xiaohui Qiu[1], Alessandra d'Azzo

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Abnormal processing of terminal sialic acids on glycoproteins changes their biochemical and functional properties, and influences cell–cell and cell–ECM communication, cell migration, and intracellular signaling, leading to loss of tissue homeostasis. The pathological consequences of glycoprotein oversialylation are evident in the severe systemic phenotypes seen in type II sialidosis, a glycoproteinosis due to deficiency of the lysosomal sialidase NEU1. As in patients with sialidosis, Neu1-KO mice develop muscle atrophy, which is uniquely triggered by progressive fibrosis of the connective tissue that invades the myofibers and causes their degeneration. We linked this phenotype to exacerbated lysosomal exocytosis, a process negatively regulated by NEU1. Increased exocytosis of lysosomal hydrolases and exosomes by Neu1-KO fibroblasts initiates a cascade of events that affects ECM integrity and tissue microenvironment. We demonstrate that Neu1-KO fibroblasts behave as myofibroblasts or mesenchymal cells: are proliferative, migratory and invasive, and have increased exocytosis of exosomes. Analyses of WT and Neu1-KO muscle, fibroblasts and exosomes showed upregulation of the TGFß and WNT/ß-catenin signaling pathways, as well as of canonical markers of epithelial-mesenchymal transition (EMT).

Remarkably, human and murine control fibroblasts can be educated to become more proliferative and invasive, by culturing them in medium conditioned with exosomes derived from Neu1-KO myofibroblasts. Thus, these microvesicles are carrier of signaling molecules that propagate the insult from cell to cell, maintaining the connective tissue myofibroblasts in a constant status of intermediate EMT. An ongoing EMT in the Neu1-KO connective tissue explains the increased proliferation of the fibroblasts, and the increased expression and deposition of ECM components, leading to a full-blown fibrosis and finally to muscle degeneration. These findings underscore the importance of NEU1-dependent upregulation of lysosomal exocytosis in the development and amplification of fibrosis. We are currently testing this paradigm in human samples from patients with fibrotic conditions of unknown etiology.

Funded in part by NIH RO1GM104981, The Assisi Foundation of Memphis and ALSAC.

COEXPRESSION OF PPCA IS ESSENTIAL FOR THE COMPLETE CORRECTION OF PATHOLOGY IN SIALIDOSIS MICE TREATED WITH RAAV- MEDIATED THERAPY

Huimin Hu, Elida Gomero, Diantha van de Vlekkert, Xiaohui Qiu, Alessandra d'Azzo

Department of Genetics, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA

Sialidosis is a glycoproteinosis caused by mutations in the *NEU1* gene. Patients present with a spectrum of clinical manifestations, affecting the systemic organs and the nervous system, and they are classified into two subtypes, type I (normomorphic) and type II (dysmorphic). The more severe type II cases share clinical features of early onset galactosialidosis. The deficient enzyme, *NEU1*, acquires full stability and activity in lysosomes only in complex with the protective protein cathepsin A (PPCA). *NEU1* $^{-/-}$ mice closely mimic human type II sialidosis. They develop similar pathological alterations in tissues and organs, and have a greatly reduced lifespan. Infertility is a fully penetrant phenotype in these mice.

In a pilot study, we have treated *NEU1* $^{-/-}$ mice by IV injection of a recombinant scAAV2/8-LP1-NEU1 vector at a dose of 1.2x10 11 vg/kg. High expression of *NEU1* was detected in the liver and kidney but not in other tissues. Instead, mice treated with scAAV2/8-CMV-NEU1(1.2x10 11) showed *NEU1* expression also in other tissues, including the brain. Histopathology showed that in the liver of treated mice lysosomal storage was completely cleared, regardless of the rAAV used, but no reversal of the phenotype was seen in the kidney and other tissues. Mice treated with either vector lived up to 7-9.5 months, and produced litters of 5-8 pups after mating with heterozygous male or female *NEU1* mice.

Interestingly, when *NEU1* $^{-/-}$ mice were injected with a combination of scAAV2/8-CMV- NEU1 (1x10 11) and scAAV2/8-CMV- PPCA (1x10 11), they exhibited much broader correction of storage vacuoles in multiple organs, including the hard-to- correct ones, such as kidneys, brain and spleen, indicating that co-expression of PPCA is needed to achieve complete reversal of the sialidosis phenotype in our mouse model. Large scale experiments are in progress to confirm these findings and to elucidate the mode of action of the two enzymes in vivo.

This work was supported in part by NIH DK095169, GM104981, Ultragenxy Pharmaceutical, Assisi foundation of Memphis and ALSAC.

ROLE OF MEMBRANE TETHERING SITES IN THE NEUROPATHOGENESIS OF GM1-GANGLIOSIDOSIS MICE

Jason Weesner, Ida Annunziata, Alessandra d'Azzo

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

GM1-gangliosidosis is a neurodegenerative lysosomal storage disease caused by deficiency of the lysosomal enzyme ß-galactosidase (ß-gal), responsible for the breakdown of the ganglioside GM1 (GM1), an important component of neuronal membranes. ß-gal loss of function results in accumulation of GM1 in the brain and spinal cord, which is at the basis of pathogenesis. *ß-gal* $^{-/-}$ mice generated by our lab faithfully recapitulate the human disease. Characterization of this model has shown GM1 accumulation at the plasma membrane (PM) and the membranes of intracellular organelles, in particular the mitochondria and ER. We found that in neurons of *ß-gal* $^{-/-}$ mice, GM1 reallocates in increased amounts to the glycosphingolipid-enriched microdomain (GEM) fraction of the mitochondrial-associated ER membranes or MAMs. The abnormal redistribution of GM1 at these tethering sites affects their individual calcium concentration and ultimately results in the activation of the unfolded protein response- and mitochondrial membrane permeabilization-induced apoptosis. We are currently investigating the effects of GM1 buildup at the PM, focusing on membrane microdomains that are formed between the PM and the ER, named PM-associated ER membranes or PAMs. Proteomic analysis of MAMs/PAMs has shown an increase in calcineurin, a calcium binding protein known to play a role in signal transduction and in the regulation of synaptic plasticity. Interestingly, we found that FK506, an inhibitor of calcineurin, rescues the mitochondrial abnormalities seen in the model, suggesting a major role of calcineurin in GM1-mediated cell death. Based on these observations, the fundamental role of calcium in synaptic plasticity, and the presence of numerous ectopic, aberrant dendrites in neurons of *ß-gal*$^{-/-}$ mice, we have initiated the analysis of the synaptosomes and the synaptic clefts in this model to assess whether an altered membrane composition due to GM1 accumulation at these sites contributes to neurodegeneration.

NEUROINFLAMMATION IN SIALIDOSIS MICE

Leigh Fremuth, Ida Annunziata, Alessandra d'Azzo

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

Sialidosis is a glycoprotein storage disease caused by deficiency of the lysosomal sialidase neuraminidase 1 (NEU1). NEU1 is responsible for removing terminal sialic acids from glycoproteins, thereby initiating their degradation. Patients with the early onset type II form of sialidosis, develop a systemic phenotype, with loss of (neuro) developmental milestones, progressive neurological abnormalities, and oligosaccharidiuria. NEU1 deficient mice (*Neu1* $^{-/-}$) recapitulate this form of sialidosis. Their brain pathology conforms with the impact of NEU1 deficiency on cells of the macrophage phagocytic system, given that microglia and perivascular macrophages are among the most affected cells. Furthermore, we found that, particularly in the hippocampus, mutant mice accumulate APP+ amyloid deposits, resembling the plaques in Alzheimer's disease (AD), making the *Neu1* $^{-/-}$ mice a potential model for sporadic AD. In this work, we are focusing on the contribution of neuroinfammation to this AD phenotype. Microarray analysis of hippocampi isolated from WT and *Neu1* $^{-/-}$ mice identified several upregulated genes coding for markers of the monocytic lineage, including microglia, macrophages and innate immune responses. Most of these upregulated genes are cell surface glycoproteins, which are likely sialylated and possible substrates of NEU1. If we prove this assumption, their altered sialic acid content may change their biochemical properties. The highest expressed genes include C3ar1, C4b, CCL3, CD33, CD68, MPEG1, and OSMR. We have confirmed their upregulation at the RNA level and are characterizing their protein expression. CD68, for instance, which plays a crucial role in phagocytosis by tissue macrophages, shows a distinct pattern of expression in *Neu1* $^{-/-}$ samples, hinting on this protein being a target of NEU1 activity. The functional characterization of the monocyte lineage in the brain of *Neu1* $^{-/-}$ mice may give us new insights on the contribution of this cell population to the development of the AD-like neurodegeneration phenotype.

TOXICITY STUDY IN GALACTOSIALIDOSIS MICE AFTER AAV-PPCA MEDIATED GENE THERAPY

Rosario Mosca, Huimin Hu, Elida Gomero, Xiaohui Qiu, Alessandra d'Azzo

Department of Genetics, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, USA

Deficiency of the lysosomal enzyme PPCA (protective protein/cathepsin A) is responsible for galactosialidosis (GS), one of the glycoproteinosis. GS patients develop a systemic condition affecting their visceral organs, muscle, bone, cartilage and nervous system. Severe nephropathy, hepato-splenomegaly, progressive ataxia and oligosaccharidiuria are hallmarks of the disease. PPCA –/– mice, an authentic model of GS, have been extensively used to test different therapeutic modalities. Here we show the results of a study on a large cohort of GS mice (~80-100) injected with three different doses of a recombinant AAV-2/8- Lp1-PPCA vector: high (2x10 13 vg/kg), medium (3x10 7 vg/kg) and low (1x10 6 vg/kg). Treated mice were euthanized at 7 days, 1, 3, 6 and 12-months post injections for collection of tissues and body fluids, in order to evaluate the therapeutic effects and potential toxicity of the rAAV vector over a prolonged period of time. Full restoration of enzyme activity was achieved in all systemic organs and remarkably, the brain with the high dose of vector, even in mice euthanized at 12-months post injection. Histopathology of the high-dose treated cohort confirmed the complete correction of tissue morphology, reversal of lysosomal vacuolization and reduction of sialylated oligosaccharides in the urine. Anatomically, all organs had a normal appearance and no pathological lesion, including ischemic, apoptotic, inflammatory or mitotic changes were noted. Assessment of the biodistribution of the rAAV vector revealed the widespread presence of virus in all organs. Treated mice showed a high tolerability of the treatment and the toxicity was negligible, and they did not show any visible difference in behavior compared with WT mice throughout the treatment period. Taken together, these results suggest that this therapy is very effective and safe and could be considered for the treatment of GS, possibly in combination with ERT that is currently progressing to the clinic.

This study is supported by grants from NIH DK095169, GM104981, Ultragenyx Pharmaceutical, The Assisi Foundation of Memphis and ALSAC.

NAGPA GENE IN BRAZILIAN MUCOLIPIDOSIS II AND III PATIENTS

Fernanda Sperb Ludwig[1,2], Malu Bettio Soares[2], Ida Vanessa Doederlein Schwartz[1,2]

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INTRODUCTION: NAGPA gene encodes N-acetylglucosamine- 1-phosphodiester-alpha-N-acetylglucosaminidase. The enzyme removes N-acetyl- D-glucosamine (GlcNAc) residues from GlcNAc-alpha- P-mannose to generate the mannose-6- phosphate (M6P) marker. Mucolipidosis II and III (ML II and III) are lysosomal disorders caused by mutations in the GNPTAB or GNPTG genes, which encode N-acetylglucosamine- 1- phosphotransferase, impairing the M6P recognition marker system. Mutations in NAGPA gene can theoretically cause ML II/III, although never reported, or could influence the severity of the phenotype of ML II/III patients. Some variants were reported as associated to stuttering and to dyslexia.

OBJECTIVE: To determine the frequency of variants in the NAGPA gene in patients with ML II/III, and their influence on the severity of the phenotype.

MATERIALS AND METHODS: Thirty unrelated patients with a clinical and genetic diagnosis of MLII (n=13) or MLIII (n= 15) or clinical and biochemical diagnosis of MLII/III (n= 2). Genomic DNA was extracted from peripheral blood. The 10 exons of NAGPA gene were amplified by PCR. Automated sequencing was performed using the automatic ABI-PRISM 3500 Genetic Analyzer. The reference sequence of NAGPA was NG_028152.1.

RESULTS/DISCUSSION: The variants identified and their respective allelic frequency were: c.333A>G (46%), c.381G>T (2%), c.683-29G>A (20%), c.920+24A>G (7%), c.920+29A>G (2%), c.920+40A>G (96%), c.1122G>A (2%), c.1174+53C>A (14%), c.1175_31-37dECCTCCTCC (40%), c.1394C>T (33%), c.1485C>T (75%), c.*139C>G (4%), c.*231C> T (55%), c.*233G>C (100%), c.*253C>T (66%) and c.*527G>A (37%). The variants do not seem pathogenic according their frequencies. Regarding variants associated to stuttering and dyslexia, only c.*527G>A was found in this sample. Variants found do not appear affect the severity of the disease.

DOSE-RANGING COMPARISON OF CHOROID PLEXUS-DIRECTED VERSUS PAN-NEURONAL-DIRECTED RECOMBINANT AAV GENE THERAPY IN A MURINE MODEL OF ALPHA-MANNOSIDOSIS

Stephen G. Kaler, Eun-Young Choi

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In a dose-ranging study of recombinant adeno-associated viral (rAAV) serotypes of variable tropism in a mouse model of alpha-mannosidosis, we compared the respective biochemical and pathological effects, and safety profiles. On administration to the cerebrospinal fluid of mice, AAV serotype 5 selectively transduces choroid plexus epithelia (CPE), specialized tissues that are unique among polarized epithelia in terms of their slow 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). Here, we compare the biochemical effects of choroid plexus-directed rAAV5 gene therapy for lysosomal acid-mannosidase (LAMAN) deficiency to that obtained with several other AAV serotypes with variable tropism for CPE, neuronal cells and glia.

We cloned the human (hu) LAMAN cDNA into a rAAV shuttle plasmid and generated recombinant AAVs expressing huLAMAN. We administered viral particles to the CSF of homozygous mutant LAMAN mice by brain lateral ventricle injection on day 3 of life at doses of 5e9, 1.6e10, or 5e10. For certain serotypes, we documented sustained restoration of LAMAN enzyme activity throughout the entire brain, despite transduction confined to CPE, lending further support to the choroid plexus hypothesis.

In a concurrent natural history study of alpha-mannosidosis patients (n=6) at the NIH Clinical Center, we noted distinctive abnormalities on brain magnetic resonance spectroscopy and magnetic resonance imaging of lumbar spine. Proteomics evaluation of cerebrospinal fluid (CSF) from these subjects revealed several candidate biomarkers potentially suitable for tracking treatment response in a future first-in-human viral gene therapy trial for this illness.

Speaker Profiles

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GENEROSO ANDRIA, M.D.

Generoso Andria organized over the years a research group at the Department of Pediatrics, University of Naples, involved in studies on genetic diseases including inborn errors of metabolism and developed all laboratory facilities necessary for biochemical and molecular investigations.

He established scientific collaborations with other institutions, both national and international, including: Baylor College of Medicine, Houston, TX, USA; Erasmus University, Rotterdam, The Netherlands; St. Louis University, St. Louis, MO, USA, St. Jude Childrens Hospital, Memphis, TN, USA; University of Colorado, Denver, CO, USA; University of Turku, Finland; University of Cambridge, UK; University of Lund, Sweden; University of Mainz, Germany; Telethon Institute of Genetics and Medicine (TIGEM), Italy. He coordinated several clinical studies on innovative treatments of metabolic diseases, including the 7th framework project EUCLYD (EUropean Consortium of LYsosomal Diseases).

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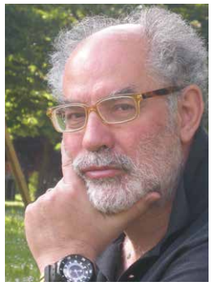
IDA ANNUNZIATA, Ph.D.

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 β-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 function, it will be possible to use them to reactivate NEU1 residual activity particularly in Type I sialidosis.



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TOMMASO BECCARI, Ph.D.

Professor Tommaso Beccari has a long experience on lysosomal enzymes that began in 1985 at the King's College of London UK in the laboratories of Prof. D. Robinson and Dr. JL Stirling, two pioneers in the field of lysosomes. He has been Visiting Professor at the King's College, London, UK; Universitè Renè Descartes, Paris, France; Georg-August-Universitat Gottingen, Germany; University of Tromso, Norway. His research has been focused on lysosomal enzymes and to study the pathophysiology of the lysosomal storage disorders, in particular alpha-mannosidosis and mucolipidosis. He has participated in the development of an enzyme replacement therapy for the lysosomal storage disease, alpha-mannosidosis. He has been the coordinator of the first pilot newborn screening for lysosomal storage diseases in Italy. More recently his research has been focused to analyse the relationship between lysosomal enzymes, Parkinson's Disease and other neurological diseases.

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Dr Bruno Bembi is Director of the Regional Coordinator Centre for Rare Diseases of the Friuli-Venezia Giulia Region and Scientific Research Coordinator at the University Hospital Santa Maria della Misericordia, Udine, Italy. Since 1985, he has been involved in and has directed clinical and research programmes in the field of lysosomal disorders.

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LINE BORGWARDT, M.D., Ph.D.

Line Borgwardt, M.D., Ph.D. at the Department of Clinical Genetics, Centre for Inherited Metabolic Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark. She graduated from University of Copenhagen in 2003. Line Borgwardt has a background in pediatric and is in specialist training (fellow) in Clinical Genetics.

In the field of metabolic diseases, her interests are mainly focused on lysosomal storage diseases. She obtained her Ph.D in Alpha-mannosidosis at the University of Copenhagen in 2015.

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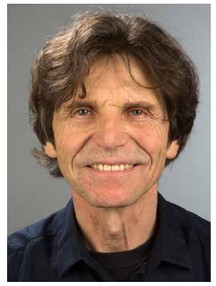
ALLISON BRADBURY

Allison Bradbury is a NRSA Postdoctoral Research Fellow in the lab of Charles H. Vite, DVM, Ph.D., ACVIM (Neurology) at the School of Veterinary Medicine at the University of Pennsylvania. She received her Ph.D. in Biomedical Sciences from Auburn University (2009-2014) with her doctoral research focused on adeno-associated virus (AAV) gene therapy in a feline model of GM2 gangliosidosis, also known as Sandhoff disease. As a NRSA Postdoctoral Research Fellow in the lab of Dr. Vite, Allison is currently evaluating gene therapy approaches in the canine model of globoid cell leukodystrophy (GLD) and feline model of mucolipidosis II (ML II).



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THOMAS BRAULKE, Ph.D.

Thomas Braulke obtained his Ph.D. 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. He established a new Department for Biochemistry at the Children's Hospital in Hamburg 1999 and is Lecturer in Biochemistry. His laboratory has a solid experience in a variety of molecular and cell biological techniques as well as 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 mucolipidosis 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 (DFG), Federal Ministry of Education and Research (BMBF), the European Community and ISMRD. At present he is the speaker of two German collaborative research groups: NCL2TREAT, and 'Mechanisms of Lysosomal Homeostasis' (FOR2625).

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LAURA CANAFOGLIA, M.D.

Dr. Laura Canafoglia obtained the Medical degree in the specialty of Neurology at the University of Milan, Italy.

She was resident and fellow at the Neurological Institute of Milan, where she was trained in Neurophysiology and Epilepsy, under the direction of Professor Giuliano Avanzini and Dr. Silvana Franceschetti.

She developed a special interest on rare diseases with epilepsy and specifically on progressive myoclonus epilepsies.

Now she is working at the Neurophysiopathology Department of the Neurological Institute of Milan, where she routinely evaluates EEG recordings and follows patients with epilepsy and myoclonic syndromes.

Recently she has developed multidisciplinary projects linking various neurophysiological and neuroimaging techniques, with the aim of studying physiopathologic mechanisms of myoclonic syndromes and ataxia.

She has participated in International and European Consortium on rare diseases to study genetic mutations of rare epilepsies and myoclonic syndromes and to share clinical and neurophysiological information.

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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 Mucolipidoses 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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XIN CHEN, M.D.,Ph.D.

Dr. Xin Chen was first awarded M.D. in Medicine from North China Coal Medical College in China and then Ph.D. in Biosignal Pathophysiology from Kobe University in Japan in 2000. He was invited to the United States of America right after graduation to work on an osteoporosis project in Dr. Edward Greenfield's lab, Case Western Reserve University School of Medicine, Cleveland, Ohio. During the 14 years of scientific research, Dr. Chen has published multiple peer reviewed papers, given many presentations, and received several awards at various scientific meetings. In 2014, he began to use rAAV8/F8 vector to treat Hemophilia mice in Dr. Paul Monahan's lab and then use scAAV9/AGA vector to treat Aspartylglucosaminuria mice in Dr. Steven Gray's lab at Gene Therapy Center, University of North Carolina at Chapel Hill, North Carolina.

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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 lysosomes 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 studying muscle development and differentiation in animal models deficient for a muscle specific ubiquitin ligase complex or its target substrates. Among Sandra's accomplishments in her research are: i) the discovery of the primary defect in galactosialidosis; ii) the identification of the 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 and sialidosis; iv) the discovery of the muscle specific ubiquitin ligase complex, OZZ-E3. A clinical trial for galactosislaidosis patients is predicted to open in the coming year. Through her seminal studies of the molecular mechanisms of disease pathogenesis in these pediatric LSD she has uncovered new functions of lysosomal enzymes and their substrates in more common adult conditions mostly associated with aging. Her research has important implications in the biology and treatment not only of LSDs but also of other adult diseases.

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ANDREA DARDIS, Ph.D.

Andrea Dardis graduated in Biochemistry and obtained a Ph.D. in Molecular Biology at the University of Buenos Aires, Argentina. Then, she obtained a specialist degree in Genetics at the University of Genoa, Italy. During her Ph.D., she was awarded a short term International Fellowship of the Lawson Wilkins Pediatric Endocrine Society to continue her training at the University of California, San Francisco (UCSF), USA. In 2000 she joined the Metabolic Unit at the Department of Paediatrics, UCSF, USA where she was working for three years as a post-doctoral fellow. In 2003 she moved to the Metabolic Diseases Unit, Pediatric Hospital "Burlo Garofolo", Trieste, Italy, as a Research Scientist. Since 2009 she is the head of the laboratory of the Regional Coordinator Centre for Rare Diseases, Udine, Italy.

She has been working in the field of metabolic diseases for more than 25 years. Her activities are mainly focused in the biochemical and molecular diagnosis of lysosomal storage diseases, the study of molecular mechanisms involved in the pathogenesis of lysosomal storage disorders and the development of novel therapeutic options for these diseases.

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BALRAJ DORAY

I have been in the field of membrane receptor trafficking for the last 17 years, first as a post-doctoral fellow, then as a Research Instructor and Assistant Professor in the Division of Hematology at Washington University School of Medicine in St. Louis. As a post-doc, my work defined the role of the GGAproteins (GGA1, GGA2, and GGA3) as being important mediators in the sorting of the mannose 6-phosphate receptor and its bound ligands from the trans-Golgi network to the endosome. Since then, I have generated various strains of knockout mice in the laboratory, namely, GGA1 null, GGA3 null, and GGA1/3 double null strains. Furthermore, I have determined that GGA2 nulls present an embryonic lethal phenotype at day 8. My present research is focused on understanding how resident Gogi proteins are retained in this organelle. My extensive experience with membrane receptor trafficking and mouse gene knockouts makes me qualified to perform research in this field.

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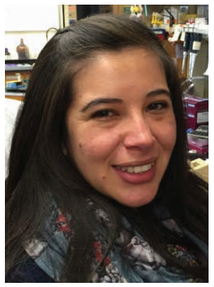
MATTHEW ELLINWOOD, Ph.D., D.V.M.

Associate Professor N. Matthew Ellinwood D.V.M., Ph.D., is a Comparative Medical Genetics Researcher at Iowa State University. He trained at Colorado State University (D.V.M. (1997; Ph.D. 2000-Physiology), with a Residency training in Veterinary Medical Genetics at the University of Pennsylvania (1998-2000) where he began his work on veterinary models of the MPS and related LSDs. He pursued a Post-Doctoral Fellowship at the University of Pennsylvania with Dr. Mark Haskins (2000-2003) in Comparative Medical Genetics, and with Dr. Philippe Moullier working in Gene Therapy at the Gene Therapy Laboratory in Nantes France. He has been at Iowa State University since 2004 where he works on neuropathic LSDs, with a special focus on MPS I and IIIB, using canine and murine models to better understand disease and better treat patients.



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NOELIA ESCOBEDO, Ph.D.

Noelia graduated with a degree in Biochemistry at the Pontificia Universidad Catolica de Valparaiso (Chile) and completed her master's degree in Biological Sciences (2008) and a Ph.D. in Cell and Molecular Biology in 2012 at the Pontificia Universidad Catolica de Chile.

In the beginnings of her scientific career, her research was focused in the area of developmental biology, in particular in analyzing the role of Syndecan-4 in Wnt/planar cell polarity during mouse development. Since then, she became fascinated with the mouse as a valuable animal model to study organogenesis in normal and pathological conditions. To pursue this goal and gain better training in this area, in 2012 she joined as a postdoctoral fellow in the laboratory of Dr. Guillermo Oliver in the Genetics Department at St Jude Children's Research Hospital (Memphis, USA). During 2012-2015 her research focused on the understanding of the role of the lymphatic vasculature during mouse development and in adult obesity using available mouse models. Subsequently, she joined the laboratory of Dr. Alessandra d'Azzo where she investigated the characteristics of the lymphatic vasculature in the lysosomal storage disease (LSD) sialidosis, and its contribution to disease pathogenesis, using a mouse model of lysosomal neuraminidase 1 (NEU1) deficiency.

She recently moved back to Chile to establish her own research group. She is currently building a research project that focuses on the role of NEU1 during mouse development and organogenesis. This study may greatly contribute to in depth understanding of sialidosis and likely other related LSDs.

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HEATHER FLANAGAN-STEET, Ph.D.

Heather Flanagan-Steet received her Ph.D. from the Department of Molecular, Cellular and Developmental Biology at the University of Colorado-Boulder in 2001. Her thesis work on skeletal muscle myogenesis sparked a life-long interest in understanding the mechanisms that control 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 and high-resolution microscopy to study early development. Her interest in the pathogenic mechanisms underlying lysosomal disease emerged through a long-time collaboration with her husband, Dr. Richard Steet. Their work - which centers around the investigation of MLII-associated cartilage and cardiac pathogenesis using zebrafish – is ongoing at the Complex Carbohydrate Research Center at the University of Georgia. Together they have begun to shed insight into the role cathepsin proteases play in early disease onset.

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JOHN FORMAN

John is a native of New Zealand, is the father of two adult twins, Timothy and Hollie, with Alpha-Mannosidosis and serves as the coordinator for research for ISMRD.

John had an early career as a union organizer and disability services provider, and for the last 25 years has built his career around the promotion of better treatment and more research on health issues, and the promotion of human rights, for those with rare disorders and disability.

John's interests include active participation in numerous nonprofit organizations, such as Lysosomal Diseases New Zealand (which he founded with his wife, Judith), the New Zealand Organization for Rare Disorders (which he also founded then managed for 15 years) and ICORD, the international Conference on Rare Disorders and Orphan Drugs. Now semi-retired, John keeps a very active interest in rare disease issues.

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RENZO GUERRINI, M.D., FRCP

Renzo Guerrini M.D., FRCP, is a Professor of Child Neurology and Psychiatry, Director of the Neuroscience Department at Children's Hospital Anna Meyer, University of Florence, Italy. He has authored over 500 Articles in peer reviewed journals, edited or authored 10 books on epilepsy and given many invited lectures throughout the world. He has served on the Editorial board of several journals and book series. Prof. Guerrini has chaired the Commission on Pediatrics of the International League Against Epilepsy and was awarded the Ambassador for Epilepsy ILAE recognition in 2003 and the Award for Research in Clinical Science by the American Epilepsy Society in 2012. He has been the principal investigator of numerous research projects and is now Coordinating DESIRE (Development and Epilepsy - Strategies for Innovative Research to improve diagnosis, prevention and treatment in children with difficult to treat Epilepsy), a major EU Research project funded by the 7th framework programme.

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THOMAS KIRKEGAARD-JENSEN, Ph.D.

My career has been focused on exploring and understanding the heat shock response and lysosomal metabolism with my main interest being in the interplay between these systems in various disease states and the development of therapies based on the understanding of these principles.

I currently hold the position of Chief Scientific Officer at Danish biotech Orphazyme ApS which was founded in 2009. Our work is focused on the cell-protective properties of the heat shock response. This natural defence mechanism can be stimulated to defend cells from a toxic accumulation of misfolded proteins or other waste products.

Today we are working to create new therapeutic approaches for a number of different diseases, including Niemann-Pick type C, Gaucher's disease, sporadic Inclusion Body Myositis (sIBM) and Amyotrophic Lateral Sclerosis (ALS).

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VISH KOPPAKA, Ph.D.

Vish is currently a Director for the Protein Sciences group in Research at Ultragenyx Pharmaceutical Inc., Novato, California. He has been with this company since 2014. He previously worked at BioMarin Pharmaceutical Inc., for more than 10 years. During this period he has worked on lysosomal storage diseases and enzyme replacement therapy.

While in academia, his research emphasis was on lipoproteins and proteins related to blood coagulation, mainly working on protein structure and function relationships. He has published in several peer-reviewed scientific journals. Dr. Koppaka has received independent funding support from both NIH and American Heart Association for his research.

Some publications:

1. Dvorak-Ewell, M., Wendt, D., Hague, C., Christianson, T., Koppaka, V., Crippen, D., Kakkis, E., Vellard, M. Melita, D-E., Enzyme replacement in a human model of mucopolysaccharidosis IVA in vitro and its biodistribution in the cartilage of wild type mice. 2010 PLoS One. 5(8):e12194: 1-11.

2. Schneeweis, L. A., Koppaka, V., Lund-Katz, S., Phillips, M.C., Axelsen, P.H. Structural Analysis of Lipoprotein E Particles. 2005 Biochemistry 44(37), 12525-12534.

3. Prince, S.W., McCormick, L.M., Wendt, D.J., Fitzpatrick, P.A., Schwartz, K.L., Aguilera, A.I., Koppaka, V., Christianson, T.M., Vellard, M.C., Pavloff, N., Lemontt, J.F., Qin, M., Starr, C.M., Bu, G., and Zankel, T.C. Lipoprotein Receptor Binding, Cellular Uptake, and Lysosomal Delivery of Fusions between the Receptor-associated Protein (RAP) and alpha-L-Iduronidase or Acid alpha-Glucosidase. 2004 J. Biol. Chem. 279, 35037-35046

4. Murray, I.V., Giasson, B.I. Quinn, S.M., Koppaka, V., Axelsen, P.H., Ischiropoulos, H., Trojanowski, J.Q., and Virginia, M. –Y. Lee. The role of the carboxy-terminus of alpha-synuclein on fibril formation in vitro. 2003 Biochemistry 42, 8530-8540.

5. Koppaka, V. Structural Studies of Discoidal Lipoprotein A-I. 2001 Cellular and Molecular Life Sciences 58, 885-893.

6. Koppaka, V., Silvestro, L., Engler, J.A., Brouillette, C.G., and Axelsen, P.H. The structure of Human Lipoprotein A-I: Evidence for the Belt model. 1999 J. Biol. Chem. 274, 14541-14544.

7. Koppaka, V., J. F. Wang., Banerjee, M., and Lentz, B.R. Acceleration of factor Xa- catalyzed prothrombin activation in solution by soluble phospholipids. 1996 Biochemistry 35, 7482-7491.

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STUART KORNFELD, Ph.D.

Stuart Kornfeld MD is Professor of Medicine at Washington University School of Medicine in St.Louis, Missouri. His research is focused on the targeting of newly synthesized lysosomal enzymes to lysosomes via the mannose 6-phosphate recognition pathway. Most recently his lab has studied how missense mutations seen in patients with MLII and MLIII impair the activity of GlcNAc-1-phospotransferase, the Golgi enzyme that generates the Man-6-P signal on lysosomal enzymes and how GlcNAc-1-phosphotransferase recognizes lysosomal enzymes as specific substrates for phosphorylation.

JEAN LEONARD

As parents, we have tackled the challenge of both our children being diagnosed with Fucosidosis. Christopher was nine months old when he had his Bone Marrow Transplant, we understand he was the first person in the world to have this operation. Christopher was born in 1991, so we hope to explain how he has enjoyed his life and tackled the many challenges along the way.

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LIN LIU, Ph.D.

During the course of my research training, I have maintained an interest in cell function, including exocytosis and endocytosis, protein or vesicle transport, signal pathway and related disease. My research training has provided me with an excellent background in cell and molecular biology, biophysics and biochemistry. As a graduate student at the joint laboratory of the Institute of Biophysics, Chinese Academy of Science and Huazhong University of Science and Technology in Beijing, China, I worked on the mechanism of the Ca2+ Release Activated Ca2+ (CRAC) channel and the function of cilia in C.elegans in Dr. Tao Xu's lab. During my first postdoctoral experience, I studied hormone release in isolated rodent and human pancreatic islets. To accomplish this, I generated a new insulin/Zinc indicator, and found it can be used to detect channelrhodopsin 2 inducted insulin secretion in pancreatic beta cells. For my second postdoctoral research, I moved into the field of biochemistry by studying the basis for the selective phosphorylation of lysosomal enzymes by the Golgi enzyme GlcNAc-1-phosphotransferase in the lab of Dr. Stuart Kornfeld. Dr. Kornfeld is an internationally recognized leader in the field of lysosomes and has an extensive record for training graduate students and postdoctoral fellows. Along with giving me new conceptual and technical training, the proposed training plan outlines a set of career development activities. We have identified the role of the various domains of GlcNAc-1-phosphotransferase in selecting lysosomal enzymes as substrates over non-lysosomal glycoproteins. During the course of this work, I developed a form of GlcNAc-1-phosphotransferase with enhanced ability to phosphorylate lysosomal enzymes, and found this property can be used to generate lysosomal enzymes that function better in enzyme replacement therapy. Currently I am studying the function of coatomer in maintaining the Golgi localization of phospohtranferase. Overall, I feel that the research project and training will give me a solid foundation for my long-term goal to become an academic researcher.

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TORBEN LÜBKE, Ph.D

Torben Lübke received his Ph.D. from the University of Göttingen in 2001 where he joined the group of Kurt von Figura and thereby came into contact with research on lysosomes and associated diseases. Since 2010, he is doing research as an associate professor in the group of Thomas Dierks, Biochemistry I at Bielefeld University on lysosomal proteins and mouse models for lysosomal storage diseases. His current projects comprise fucosidosis & novel lysosomal sulfatases.

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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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DAG MALM, M.D., Ph.D.

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

He has been:

Assistant Professor at the Institute of Clinical Medicine, University of Tromsö, Norway (UiT) 1986 - 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 Tromsö Centre of Internal Medicine which he leads.

He became a specialist in Internal Medicine in 1985, in Gastroenterohepatology in 1990 and obtained a Ph.D. 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 "Tromsö 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 Tromsö 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 humans 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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ENRICO MORO, B.SC., Ph.D.

University of Padova, Padova, Italy - B.Sc - 03/14/1996 - Gene Therapy
University of Ferrara, Ferrara, Italy - PhD - 12/12/2001 - Reproductive Biology & Endocrinology
Cedars Sinai Medical Center, UCLA, USA - Post-Doc - 2002-2003 - Cell Biology and Endocrinology
University of Padova, Padova, Italy - Post-Doc - 2004-2011 - Cell Biology, Developmental Biology
University of Padova, Padova, Italy - Assistant Professor - 2011-present - Lysosomal Storage Disorders

I authored 53 full-length publications in peer-reviewed journals, including Endocrine Reviews, Lancet, and PNAS. I was co-editor of two special issues of the J Endocrinol Invest. Total Impact factor 282; mean impact factor 5.32; h-index (source ISI Web of Science) 22. Since my Ph.D. training (1997), I have been always involved in studies related to human disorders. From 1997 to 2003, I have been involved in the characterization of DNA rearrangements, particularly microdeletions, occurring in the Y chromosome of male infertile patients. During this period I published a consistent number of papers, unveiling the involvement of specific germ-cell related genes in male infertility. During the following seven years, in my post-doc at the UCLA in California and at the University of Padova (Italy) I was involved in strategic projects concerning the role of pancreatic genes in the onset of human diabetes. Among my major research achievements were the discovery of an important role of the oncogene PTTG in pancreatic beta cell proliferation (2003) and the identification of IRX3, as a candidate gene associated with obesity and type 2 Diabetes (2010). In the past six years my research efforts have been addressed to the analysis of Lysosomal Storage Disorder (LSD) pathogenesis. In particular, I have started to use the zebrafish model to understand the early pathogenic steps, underlying the peculiar spectrum of LSD defects. I have focused my work on MPSII (Hunter syndrome) and Gaucher disease (GD), both characterized by skeletal abnormalities. Together with my team, we have generated two distinct fish models for MPSII and GD, analyzing the early onset of well-defined cell signaling alterations involved in heart and bone defects of MPSII fish and skeletal abnormalities of GD fish. While for MPSII we have recently demonstrated a key role of the Sonic Hedgehog pathway in the cardiac pathogenesis (2017), in the GD field we have previously documented an impairment of the canonical Wnt signaling preceding a primary osteogenic defect (2015). In collaboration with the Telethon Biobank held by Dr. Mirella Filocamo at the Gaslini Institute in Genova (Italy), we have been carrying out a systematic analysis of DNA samples from GD and MPSII patients to identify key molecular markers of disease pathogenesis.

My research work has been funded by the Italian Ministry of Health (2010) and the Genzyme-Sanofi Company (2012-2017). I was invited to speak at 16 international and national meetings. I took part in the European Quality Control for Y Chromosome Deletions detection in 1999 and awarded in 2014 by the European Working Group for the Gaucher Disease (EWGGD).

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AMELIA MORRONE, BS, Ph.D.

Amelia Morrone is Associate Professor at the Paediatric Neurologic Unit of the University of Florence, Italy. She is also the Director of the Molecular and Cell Biology Unit at the Meyer Children's Hospital in Florence.

She obtained her Bachelor of Science degree in Biology at the University of Florence. She received her Ph.D. in Neurometabolic Science at the University of Florence and has specialized in Medical Genetics as well as in Biochemical and Clinical Biochemistry. She worked as a PhD student with Dr. Sandra D'Azzo (Rotterdam, Netherlands) and Dr. Eric P. Hoffman at the Department of Molecular Genetics and Biochemistry, Pittsburgh (PA, USA).

Prof. Morrone has great experience in the area of lysosomal storage disorders (LSDs), working on molecular and cell biological characterisation of the normal and mutant lysosomal enzymes. She has been also PI on several research programs on the genetics of neuromuscular diseases, urea cycle disorders, organic acidurias and amino acids disorders.

She collaborates with various National and International Centres on research projects in the field of Inborn Errors of Metabolism including LSDs.

She is a member of the European Working Group on Lysosomal Disease, the Society for the Study of Inborn Errors of Metabolism, the Italian Society of Human Genetics and the Italian Society of Metabolic Disorders.

Prof. Morrone has published numerous peer-reviewed articles and book chapters in the field of metabolic diseases.

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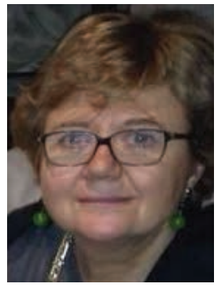
JENNY NOBLE

Jenny Noble is the mother of two adults Hayden and Sarah who have Mucolipidosis III alpha/beta (Pseudo-Hurler Polydystrophy).

Since the diagnosis of her two children Jenny has spent many years searching and advocating for innovative ways to manage the complications of Mucolipidosis. Through this advocacy Jenny has built up strong international networks with professionals, families and other support groups to improve outcomes for families with Lysosomal Diseases.

Jenny is currently a Field Officer and Administrator for Lysosomal Diseases New Zealand and has been in this role since 1999. Jenny joined the ISMRD Board of Directors in 2004. Though not trained in health or science, she is one of the co-authors of *The Osteodystrophy of Mucolipidosis Type III and the Effects of Intravenous Pamidronate Treatment* published in the Journal of Inherited Metabolic Diseases.



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ROSSELLA PARINI

Dr. Parini is member of several international and national scientific societies or study groups, including the Society for the Study of Inborn Errors of Metabolism (SSIEM), the American Society of Human Genetics (ASHG), the European Study Group for Lysosomal Disorders (ESGLD) and the Italian Pediatric Society (SIP), Pediatric Clinical Genetics (SIMGEPED) and Human Genetics (SIGU). She is part of the scientific board of the Hereditary Metabolic Diseases and neonatal screening (SIMMESN).

As a board member, she is active in patients' associations and disease registries: she is member of the Italian MPS Society (AIMPS) scientific advisory Board and of the Italian Fabry disease society (AIAF) scientific advisory board; she participates in the MPS I European Board supported by Genzyme, the Fabry Outcome Survey (FOS) Pediatric task force and the Hunter Outcome Survey (HOS) board both supported by Shire and the MPS VI Clinical Surveillance Program advisory board supported by BioMarin. Her publication list contains many articles, of which the vast majority have been published in English-language, peer-reviewed journals: 155 publications in PubMed. She is (co-)author of 45 publications in the last 4 years. She has authored several Italian book chapters and reviews on metabolic disorders.

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FRANCES PLATT, Ph.D.

Department of Pharmacology, University of Oxford, Oxford, UK

Prof. Frances Platt obtained her Ph.D. from the University of Bath, UK, and was a post-doctoral fellow at Washington University Medical School in St. Louis, USA. She was a Lister Institute Senior Research Fellow and is currently Professor of Biochemistry and Pharmacology in the Pharmacology Department at the University of Oxford. Her main research interests include the biology and pathobiology of glycosphingolipids, in particular glycosphingolipid lysosomal storage diseases. Her research led to the development of the approved drug miglustat for the treatment of glycosphingolipid storage diseases. Prof. Platt was awarded the Alan Gordon Memorial Award and the Horst Bickel Award for advances in metabolic disease therapy. She was elected a fellow of the Academy of Medical Sciences in 2011, is a Trustee of the Gordon Research Conferences and serves on the board of several international rare disease charities.

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PAUL SAFTIG

Prof. Dr. Paul Saftig is director of the Biochemical Institute at the Christian Albrechts-University in Kiel located in the north of Germany.

His scientific career started in the lab of Kurt von Figura, University Göttingen where he completed his Ph.D. thesis, postdoctoral phase and habilitation. His major research interests are lysosomes, lysosomal membrane proteins and lysosomal storage disorders.

Another aspect of his research is the biology of proteases playing a role in intramembrane proteolysis or in proteolytic events happening at the plasma membrane. In 2011 he received the highest German award for his discoveries related to the function of proteases involved in Alzheimer's Disease. He published a number of milestone discoveries in areas of lysosome biology, neurodegenerative diseases and protease research.

Dr. Saftig has published more than 250 original research papers and a number of hightly cited review articles.

Since 2000, he is participating and chairing national and European networks dedicated to develop therapies for lysosomal storage disorders.

University Medical Center
Hamburg-Eppendorf
Germany

ANGELA SCHULZ

Angela Schulz has been the Head of the research group for childhood neurodegenerative disease at the University Medical Center Hamburg-Eppendorf, Hamburg, Germany since 2015.

Dr. Schulz received her medical degree from the Albert-Ludwigs-Universität, Freiburg in 2000. After a one year medical sub-internship at the University of Tampa, Tampa, FL, USA, she completed her junior (2001-2003) and senior residency (2006-2011) at the Children's Hospital, University Medical Center Hamburg. Between her two residencies, she was a postdoctoral research fellow at the Department of Pediatric Neurology at Duke University Medical Center, Durham, NC, USA. Dr. Schulz obtained board certification in paediatrics and clinical specialisation in paediatric palliative care medicine in 2011.

Her main research interests are paediatrics, neurology and neurodegeneration, investigating rare paediatric neurodegenerative diseases, especially lysosomal storage diseases like neuronal ceroid lipofuscinoses (NCL).

Dr. Schulz is principal investigator of several clinical studies in the area of rare diseases, e.g. studies on intracerebroventricular enzyme replacement therapy (ERT) in patients with CLN2 disease and on intrathecal ERT in patients with mucopolysaccharidosis type IIIA. She received a research award of the German Society for Pediatric Neurology in 2005. From 2011 to 2014, Dr. Schulz acted as coordinator for the European FP7 project DEM-CHILD. She is also work package lead of the European Horizon 2020 project BATCure and the BMBF-funded National NCL Research consortium NCL2TREAT.

Dr. Schulz has authored and co-authored many peer-reviewed publications and contributed to the patent application on a method for diagnosis of NCL.

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RICHARD STEET, Ph.D.

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

Professor Dr. Ritva Tikkanen

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RITVA TIKKANEN, Ph.D.

Ritva Tikkanen obtained her M.Sc. in Biochemistry (University of Turku, Finland), and received her Ph.D. from the University of Helsinki, under the supervision of late Leena Peltonen-Palotie. Thereafter, she went to the laboratory of Kurt von Figura to Göttingen, Germany, as a Marie Curie Fellow, and then started establishing her own group at the University of Bonn. She joined the faculty of the University of Frankfurt am Main as an Assistant Professor of Biochemistry in 2003. Since 2008, she is a full professor of Biochemistry and Molecular Biology at the Medical Faculty of the Justus-Liebig University of Giessen.

Already very early in her career, Ritva gained interest in lysosomal storage disorders and did her Ph.D. work on the structure-function relationship of the lysosomal hydrolase, aspartylglucosaminidase (AGA). She has remained in the field of lysosomes all through her career, studying mainly endosomal and lysosomal trafficking of proteins and cancer cell signaling. Her lab is also interested in skin biology and the autoimmune disease Pemphigus vulgaris. A few years ago, she went back to her scientific roots and picked up the work on AGA again. Currently, many members of her lab are working on the lysosomal storage disorder AGU that is caused by the deficiency of AGA and for which no therapy is currently available. Recently, her group was able to develop a potential novel therapy for AGU, based on the use of pharmacological chaperones (PC). This therapy is suitable for many patients, including those that carry the world-wide most common AGU mutation, AGUFIN, and a clinical trial is soon to start in Finland with this compound. Her lab is also aiming at developing personalized therapies for patients exhibiting mutations that do not benefit from the PC treatment, such as nonsense mutations and splicing defects. Further work in her lab will aim at developing enzyme replacement therapy for AGU with an enzyme formulation that is able to cross the blood-brain barrier. Ritva and her lab team are dedicated to finding a suitable treatment for all patients suffering from this tragic disease.

CAMILO TORO, M.D.

Camilo Toro, is a Clinical Neurologist at the National Institutes of Health (NIH) in Bethesda Maryland. Dr. Toro is a member of the clinical team at the Undiagnosed Diseases Program (UDP). Dr. Toro has interest in the diagnosis of rare neurological disorders and the characterization of neurological issues that accompany rare metabolic and genetic disorders. Dr. Toro will be speaking on the spectrum of neurological problems in CHS, their possible cause and potential management strategies.

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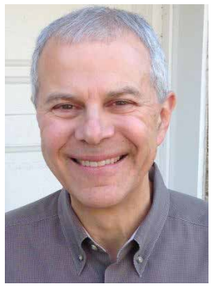
GEPKE VISSER, M.D., Ph.D.

Gepke Visser, paediatrician, is head of the department of metabolic diseases of the Wilhelmina Children's Hospital, UMCU in The Netherlands. Her hospital hosts the designated Dutch hematopoietic stem cell transplantation centre for lysosomal storage disorders in which she actively participates. She also coordinates the Dutch Diagnosis Regisitry Metabolic Disorders (www.ddrmd.nl) a registry in which all Dutch metabolic centres participate. This registry contains data on patients diagnosed and treated with an inherited metabolic disorder in the Netherlands and also on outcome of the national newborn screening program on metabolic disorders.

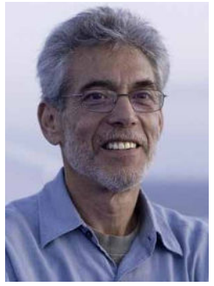


ISMRD Board Member

PAUL WAGNER

Paul is a father of four and a grandfather of two, one of whom is affected by Mucolipidosis II. Before retiring in 2014, Paul held leadership positions in IT (Crate and Barrel, Wolters Kluwer), Marketing (Wolters Kluwer), and Fundraising (WTTW/Chicago's Public Television station).

Since retiring Paul has enjoyed traveling with his wife, Susie, spending more time with his children, sitting for his grandchildren and being involved with several philanthropic organizations. He looks forward to the time when no families will have to contend with any of the glycoprotein storage diseases.



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DAVID WENGER, Ph.D.

David Wenger initially trained to be a pharmacist however after completing pharmacy school he knew he did not want to be a pharmacist. He decided to get a Ph.D. in biochemistry at Temple University School of Medicine. A course in human genetics sparked his interest in human genetic disorders. His PhD research involved studies on glycolipid metabolism in myelin in the developing mouse brain. After two postdoctoral fellowships, one in organic chemistry at the Weizmann Institute and one in neuroscience at UCSD, he joined the Department of Pediatrics at the University of Colorado Medical School in 1971 and started a laboratory dedicated to understanding certain lysosomal disorders. His first NIH grant was to study the substrate specificity of human beta-galactosidases, including acid ß- galactosidase and galactocerebrosidase (GALC). It was only in 1970 that the genetic defect in Krabbe disease, GALC, was identified. While that opened up enzyme-based testing in suspected patients using a blood sample, no one had purified the GALC enzyme and, of course, the gene was not cloned. In 1973 he started the Lysosomal Diseases Testing Laboratory. This laboratory has diagnosed over 4600 patients with a lysosomal disorder, the most in the world. With much effort over many years he purified GALC and cloned the cDNA and gene in 1993. He was helped tremendously by a postdoctoral fellow from China, Yue Qun Chen, who unfortunately died in 1993 from cancer. This immediately allowed the laboratory to start looking for mutations in patients. The laboratory identified the 30 kB deletion, the most common mutation in the European population, and about 60 other mutations. Studies were started showing that GALC cDNA placed in cells in culture resulted in the expression and secretion of GALC into the media and uptake by neighboring cells. This is the basis for cell and gene therapy currently underway in this and other laboratories. The availability of animal models has given them a valuable tool to evaluate treatment options. Information from the researchers who study viral vectors for other disorders provided information very useful for choosing a vector that can treat both the central and peripheral nervous systems affected in Krabbe disease. Studies from this laboratory and others showed that a class of viral vectors called adeno-associated viral (AAV) show the most promise. Current research is centered on using a vector called AAVrh10 containing the mouse GALC cDNA both alone and in combination with bone marrow transplantation in the twitcher (twi) mouse model of Krabbe disease. A single iv injection of this vector shows great promise in delaying the onset of clinical findings, improving myelination and delivering GALC activity to all nervous tissues, including the peripheral nervous system. Since hematopoietic stem cell transplantation in pre-symptomatic and mildly affected later-onset individuals with Krabbe disease is the current "standard of care", the addition of a single iv injection of this viral vector to the treatment

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Speaker Profiles

protocol could provide a large boost to the effectiveness of treatment. This iv-injected vector rapidly provides GALC activity to all critical tissues while the blood stem cells improve the inflammatory component found in this disease. Most affected twi mice undergoing this treatment are doing very well (average survival is about one year vs 40 days if untreated). Some treated mice lived two years. Additional toxicology studies are underway before human trials can begin. These and other studies indicate that safe and effective additional treatment for patients with Krabbe disease and other lysosomal disorders is rapidly approaching.

Delegates

Parents			
Last Name	First Name	Disorder	Country
Addinall	Joanne	Family Member	England
Bricca	Giovanna	Sialidosis	Italy
Bricca	David	Sialidosis	Italy
Catozzi	Luis	Mucolipidosis III	Italy
Catozzi	Emanuela	Mucolipidosis III - Parent	Italy
Catozzi	Luciano	Mucolipisosis III - Parent	Italy
Catozzi	Maryuri	Sibling	Italy
Cruz	Jorge	Spanish MPS Society	Spain
Garcia	Ivan	Galactosialidosis	United States
Garcia	Melody	Sibling	United States
Gregoriades	Anne	Alpha Mannosidosis	France
Hausleitner	Andrea	Fucosidosis - Parent	Austria
Hausleitner	Robert	Fucosidosis - Parent	Austria
Hausleitner	Helena	Fucosidosis	Austria
Incardona	Hermance	Aspartylglucosaminuria	France
Incardona	Stephane	Aspartylglucosaminuria - Parent	France
James	Jackie	President ISMRD	United States
Jamil	Samuel	Mucolipidosis III	England
Jamil	Shirley	Mucolipidosis III - Parent	England
Jamil	Shamim	Mucolipidosis III - Parent	England
Jamil	Edward	Sibling	England
Jamink	Darko	Mucolipidosis III - Parent	Slovenia
Jamink	Mojca	Mucolipidosis III - Parent	Slovenia
Josette	Redon	Family Member	France
Khalil	Lama	Family Member	Saudi Arabia
King	Kathleen	Alpha Mannosidosis - Parent	United States
Knaggs	Louise	Mucolipidosis II	England
Leonard	Jean	Fucosidosis	England
Leonard	David	Fucosidosis	England
Leonard	Christopher	Fucosidosis	England
Mikuitiene	Donatas	Alpha Mannosidosis - Parent	England
Mikutaite	Emma	Alpha Mannosidosis	England
Mikutaite	Sofia	Sibling	England
Mikutiene	Gintare	Alpha Mannosidosis - Parent	England
Nicola	Cocconi	Family Member	Italy
Noble	Paul	Mucolipidosis III - Parent	New Zealand
Noble	Jenny	Vice President ISMRD	New Zealand
Paisley-Dew	Carolyn	Board Member - ISMRD	Australia
Pauls	Ashley	Galactosialidosis	United States
Peach	Daniel	Sialidosis	New Zealand
Peach	Faith	Sialidosis	New Zealand
Posdijk	Ciska	Family Member	Netherlands
Qashou	Tareq	Family Member	Saudi Arabia
Qashou	Rayan	Fucosidosis	Saudi Arabia
Qashou	Moutaz	Sibling	Saudi Arabia
Qashou	Youssef	Sibling	Saudi Arabia
Roll	Pernille	Mucolipidosis III	Norway
Roll	Truls	Mucolipidosis III - Parent	Norway
Roll	Birthe	Mucolipidosis III - Parent	Norway
Roll	Stine	Sibling	Norway
Roll	Mia	Sibling	Norway
Scott	Martin	Fucosidosis	England
Sluga Jamnik	Ziga	Mucolipidosis III	Slovenia
Sluga Jamnik	Dasa	Sibling	Slovenia
Stark	Robert	Alpha Mannosidosis	United States
Stark	Mark	Board Member - ISMRD	United States
Stark	Matthew	Sibling	United States
Stephanie	Armand	Family Member	France
Taravella	Alexander	Aspartylglucosaminuria	United States
Taravella	Daniel	Aspartylglucosaminuria	United States
Taravella	Julia	Aspartylglucosaminuria - Parent	United States
Van Dam	Richard	Mucolipidosis III - Parent	Australia
Van Dam	Jesse-Rose	Mucolipidosis III	Australia
Van Dam	Damion	Mucolipidosis III	Australia
Van Dam	Juanita	Mucolipidosis III - Parent	Australia
Wagner	Paul	ISMRD Board Member	United States
Westerink	Marinus-Jan	Family Member	Netherlands
Westerink	Dorenda	Sialidosis	Netherlands
Westerink	Hannah	Sialidosis	Netherlands
Woolley	Saffron	Alpha Mannosidosis	England
Woolley	Martin	Alpha Mannosidosis - Parent	England
Woolley	Sonja	Alpha Mannosidosis - Parent	England

Professionals/Industry			
Ali	Qais Abu		United States
Andersson	Claes	Zymnex	Sweden
Andria	Generoso	University of Naples	Italy
Annunziata	Ida	St Judes Research Hospital	United States
Beccari	Tommasco	University of Perugia	Italy
Bembi	Bruno	Centre for Rare Diseases	Italy
Bogwardt	Line	Copenhagen University Hospital	Denmark
Bradbury	Allison	Complex Carbohydrate Research Centre	United States
Braulke	Thomas	Univeresity Medical Centre Heamburg	Germany
Brink-Kjzr	Tove	Copenhagen University Hospital	Denmark
Canafogila	Laura		Italy
Cathey	Sara	Greenwood Genetic Center	United States
Chen	Xin	University of North Carolina	United States
Dardis	Andrea	Centre for Rare Diseases	Italy
d'Azzo	Alessandra	St Judes Research Hospital	United States
Dickson	Patricia		United States

Delegates

Doray	Balraj	Washington University	United States
Ellinwood	Matthew	Iowa State University	United States
Ericsson	Annika	Zymnex	Sweden
Escobedo	Noelia	St Judes Research Hospital	United States
Fermuth	Leigh	St Judes Research Hospital	United States
Flagagan-Steet	Heather	Complex Carbohydrate Research Centre	United States
Flumara	Agata	University of Catania	Italy
Gomero	Elida	St Judes Research Hospital	United States
Guerrini	Renzo	University of Florence	Italy
Heymann	Anette	Chiesi	Denmark
Hu	Huimin	St Judes Research Hospital	United States
Hyden	Pia	Zymnex	Sweden
Kirkegaard-Jensen	Thomas	Orphazyme	Denmark
Koppaka	Vish	Ultragenyx	United States
Kornfeld	Stuart	Washington University	United States
Lampe	Christina		Denmark
Langseth	Geir		Norway
Laulund	Charlotte		Denmark
Liu	Lin	Washington University	United States
Loeb	Elizabeth	Washington University	United States
Lubke	Torben	University of Bielefeld	Germany
Lund	Troy	University of Minnesota	United States
Malm	Dag	Tromso Centre	Norway
Moro	Enrico	University of Padova	Italy
Morrone	Amelia	University of Florence	Italy
Mosca	Rosario	St Judes Research Hospital	United States
Natesan	Arjun		United States
Parini	Rossella	Pediatrician and Geneticist	Italy
Petersen	Kelli		United States
Platt	Frances	University of Oxford	England
Procopio	Elena		Italy
Pulles	Tom	Ultragenyx	Europe
Qiu	Xiaohui	St Judes Research Hospital	United States
Saftig	Paul	University of Kiel	Germany
Scarpa	Maurizo	University of Padova	Germany
Schulz	Angela	University Medical Centre Hamburg	Germany
Schwartz	Ida		Brazil
Siham	Hallal	Student Dr.	Algeria
Snanoudj-Verber	Sarah	UNC Gene Therapy Centre	France
Steet	Richard	Complex Carbohydrate Research Centre	United States
Tiede	Stephan	Hamburg	Germany
Tikkanen	Ritva	University of Giessen	Germany
Toro	Camilo	National Institute of Health	United States
van de Vlekkert	Diantha	St Judes Research Hospital	United States
Visser	Gepke	University Medical Center Utrecht	Neitherlands
Weesner	Jason	Student Dr.	United States
Weigelt	Cecilia	Zymnex	Sweden
Wenger	David	Lysosomal Diseases Tresting Laboratory	United States
Yang	Zhang	University of Copenhagen	Denmark

Notes

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