Welcome
to
San Antonio

amda

IPA
International Pompe Association

2015 AMDA-IPA International Pompe Patient and Scientific Conference Brochure

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Welcome to the Conference!

On behalf of the Acid Maltase Deficiency Association (AMDA), the International Pompe Association (IPA) and the city of San Antonio, I would like to welcome you all to the 2015 AMDA/IPA Pompe Patient and Scientific Conference!

I am very excited to announce that we are expecting over 170 Conference participants from 14 countries at the Conference! This will be the largest AMDA/IPA Pompe Patient and Scientific Conference in history, and all credit should go to the energy and support of the Scientific/Medical Community, the Patient Community, and Industry.

As the International Pompe Day slogan says: "Together We Are Strong!"

It is my sincere hope and belief that our time together over the next few days will once again show the world how strong the Pompe Community really is! I think we have already made a great start, and I believe that our interactions and our sharing of ideas and information will show what we can accomplish when we work together.

Robert H. Goddard said: "The dreams of yesterday are the hopes of today and the reality of tomorrow." Over the last twenty (20) years the AMDA has seen a treatment for Pompe disease become a hope, and then a reality. Gene therapy and next generation treatments are among just a few hopes and dreams that will be discussed during the Conference. Only time will tell which hopes become tomorrow's realities. But, it will continue to require that we all work together for the best interests of the Pompe Community.

I look forward to hearing the presentations, seeing old friends, and meeting new friends at this year's Conference, as I'm sure you do, too.

I hope you all have a good time.

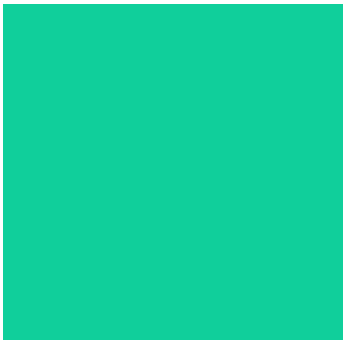
Tiffany House

AMDA President
IPA Chair

A very special THANK YOU to Marsha Zimmerman, AMDA Patient Advocate!

Marsha has been instrumental in helping to organize the Conference; from keeping track of Conference Registrations, to organizing special surprises for Conference attendees, to coordinating with the University of Texas at San Antonio Health Science Center Continuing Medical Education office. Her help and support has been indispensible.

Thank you Marsha!



Helpful Tips and Information

General Information

All presentations and meals during the main body of the Conference will take place on the 7th Floor of the Holiday Inn Riverwalk.

The program is rather packed, and the schedule is tight. We rely on your cooperation as a Speaker and/or Attendee to help us stay on schedule. Please stick to the scheduled times, so that all topics can be covered and addressed.

CME Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The UT Health Science Center San Antonio School of Medicine and the Acid Maltese Deficiency Association. The UT Health Science Center San Antonio School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The UT Health Science Center San Antonio School of Medicine designates this live activity up to a maximum of 8.75 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Academy of Physician Assistants (AAPA), American Academy of Nurse Practitioners (AANP) and the American Nurses Credentialing Center (ANCC) accepts certificates of participation for educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by the ACCME.

Healthcare professionals receiving a certificate of attendance should consult with their licensing board for information on applicability and acceptance.

CME Evaluations & Certificates

Keep track of your continuing medical education credits on your Record of Attendance. The paper document is for your record only. Please do not turn in the Record of Attendance form at the end of the conference. An account has been set-up for you to obtain your CME certificates online.

Following the Workshop visit the CME website, cme.uthscsa.edu, for evaluation and certificate information.

a. click on the Post Conference tab

b. click on 2015 AMDA/IPA Pompe Conference

Ground Rules

- Please turn your cell phones OFF during the Sessions
- Please use a microphone when asking questions
- Be concise in questions and discussions to allow for contributions from as many people as possible.
- Please help us stay on time and stick to the schedule

Halloween Corner

On Oct. 31 from 1-5 PM we will have some fun Halloween crafts and activities for Kids (of all ages!) in the Bolero 2 Room. Stop by and check it out!

Share Your Story

The AMDA is taking the unique opportunity of having so many from the Pompe Community in one place and is asking for volunteers to share their Pompe story.

How were you diagnosed? What messages do you have for the newly

Halloween Activities

There are a variety of fun Halloween activities taking place in Downtown San Antonio. Below is a short list of some options. Please ask the hotel staff for additional suggestions.

- **AMDA Halloween Reception and Riverboat Tours:** The AMDA has Riverboats to take Conference Attendees on tours of the Riverwalk. Tours will be from 7:30-8:30 and 8:30-9:30 (weather permitting!). Space is limited, so reserve your spot at the AMDA Table in the Exhibit Room! There will also be an AMDA-sponsored Halloween Reception from 7-9 PM. Come grab a bite to eat, and have a Spooky Good Time on the Riverwalk! Heavy appetizers and a Cash Bar will be provided.
- **River Walk Halloween Fest** (see Flyer on the right)
- **Movies by Moonlight–Terror in Travis Park** (see flyer below)
- **More Delightful than Frightful @ Morgan's Wonderland** (see flyer below)
- **13th Floor Haunted House:** 1203 E. Commerce St. San Antonio, TX 78205

Conference Agenda

October 30, 2015 – November 1, 2015
San Antonio, Texas

Friday, October 30th, 2015

Conference Registration 4:00-6:00
7th Floor of Holiday Inn
Welcome Dinner 6:00-9:00
(meet in the Lobby of the Holiday Inn at 6 PM)

Saturday, October 31st, 2015

Breakfast 7:00–8:00

Welcome Addresses 8:00-8:15
The Natural History of Pompe Disease 8:15-8:45
Dr. Hannerieke van den Hout (Erasmus University)
Question and Answer 8:45-8:55

IPA/Erasmus Survey and Pompe Registry
Ten years of the International Pompe Survey 8:55-9:15
Dr. Chris van der Meijden (Erasmus University)
Report from Genzyme's Pompe Registry 9:15-9:35
Dr. Virginia Kimonis (Univ. of California-Irvine)
Question and Answer 9:35-9:45

Break 9:45-10:00

Diagnosis, Management, and Treatment of Pompe
Diagnosis and Genetic Counseling in Pompe 10:00-10:20
Dr. Deeksha Bali and Stephanie Austin (Duke University)
Patient Management & Current Standard of Care 10:20-10:40
Dr. Priya Kishnani (Duke University)
Respiratory Management of Pompe 10:40-11:00
Dr. John Bach (New Jersey Medical School)
Diaphragm Pacemaker Presentation 11:00-11:20
Dr. Barbara Smith (Univ. of Florida-Gainesville)
Results from Pompe Exercise Study 11:20-11:40
Dr. Ans van der Ploeg (Erasmus University)
Question and Answer 11:40-12:00

Lunch 12:00-1:00

Parent Perspective
Living a "Normal" Pompe Life 1:00-1:20
Krystal Hayes
Question and Answer 1:20-1:30

Gene Therapy
Introduction by Dr. Arnold Reuser (Erasmus University) 1:30-1:45
Dr. Andrea Amalfitano (*Michigan State University*) 1:45-2:00
Dr. Barry Byrne *(Univ. of Florida-Gainesville)* 2:00-2:15
Dr. Dwight Koeberl *(Duke University)* 2:15-2:30
Dr. Pim Pijnappel *(Erasmus University)* 2:30-2:45
Question and Answer 2:45-3:00

Break 3:00-3:30

ERT: What Have We Learned So Far Roundtable
Introduction by Tiffany House 3:30-3:40
Dr. Yin-Hsiu Chien (*National Taiwan Univ. Hosp.*) 3:40-4:00
Dr. Priya Kishnani *(Duke University)* 4:00-4:20
Dr. Benedikt Schoser *(Friedrich-Baur-Institute)* 4:20-4:40
Dr. Ans van der Ploeg *(Erasmus University)* 4:40-5:00
Open Discussion with Audience 5:00-6:00

Sunday, November 1st, 2015

Breakfast 7:30-8:30

Future Research
Pompe disease: Pathophysiology and novel approaches to therapy 8:35-8:55
Dr. Nina Raben (National Institute of Health)
Stem Cell Presentation 8:55-9:15
Dr. Pim Pijnappel (Erasmus University)
GAA genotypes: What Do They Tell Us? 9:15-9:35
Dr. Arnold Reuser (Erasmus University)
Modifying Factors 9:35-9:55
Dr. Cesare Danesino (University of Pavia, Italy)
Biomarkers in Pompe Disease 9:55-10:15
Dr. Giancarlo Parenti (Federico II University, Naples)
Question and Answer 10:15-10:45

Break 10:45-11:15

Industry Updates
Amicus Therapeutics 11:15-11:30
Nita Patel, Director Patient & Professional Advocacy
Audentes Therapeutics 11:30-11:45
Dr. Suyash Prasad, Chief Medical Officer
Biomarin Pharmaceutical 11:45-12:00
Dr. Liron Walsh, Medical Director
Genzyme Corporation 12:00-12:15
Dr. Susan Sparks, Medical Director Genetic Diseases
Oxyrane 12:15-12:30
Dr. Wouter Vervecken, Chief Technology Officer
Question and Answer 12:30-1:00

Lunch 1:00-1:30

Conference Close

Planning Committee Biographies

Thank you for your help!!

Dr. Jannine Cody, M.D., Ph.D.

Jannine is originally from Charles City, Iowa. At the University of Iowa she earned a B.S. degree in General Science and a M.S. degree in Biology.

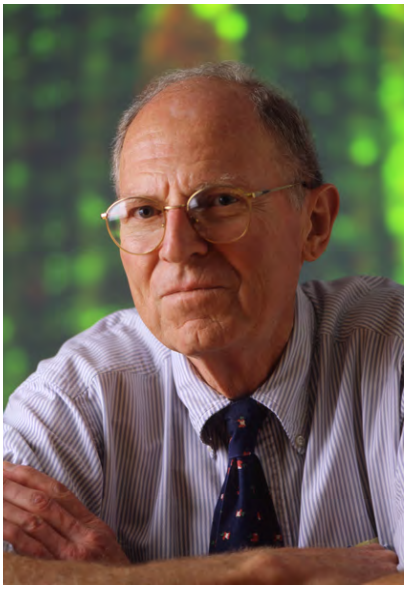
In 1990, Jannine founded the Chromosome 18 Registry and Research Society as a way to bring affected families together and to learn from each other. To date, the Registry includes more than 3000 families affected by chromosome 18 abnormalities from around the world. In 1991, Jannine enrolled in a Ph.D program at the University of Texas Health Science Center at San Antonio; graduating in 1997. Jannine is now a Professor in the Department of Pediatrics at the UT Health Science Center at San Antonio.

While pursuing her Ph.D., she developed the multidisciplinary Chromosome 18 Clinical Research Center, the goal of which is to make the chromosome 18 conditions completely treatable. The research ranges from the molecular biology of the conditions, to the clinical consequences, to the psychosocial ramifications for the affected individual, the parents and the siblings. This work is primarily funded by the families of the Chromosome 18 Registry.

In an effort to ensure federal support for research into chromosome abnormalities, Jannine has testified twice before the US Congress and has served on a variety of national committees and organizations related to genetics.

Jannine's current positions are:

- Founder and President, The Chromosome 18 Registry & Research Society
- Professor of Pediatrics, University of Texas Health Science Center at San Antonio (UTHSCSA)
- Director of the Chromosome 18 Clinical Research Center; Department of Pediatrics, UTHSCSA
- Scientific Director, Pediatric Clinical Research, Department of Pediatrics and Institute for the Integration of Medicine and Science, UTHSCSA



Dr. Paul Plotz, M.D.

Prior to his retirement in early 2011, Dr. Plotz had been a member of the Arthritis and Rheumatism Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the National Institutes of Health for more than four decades. Both his clinical and his research work for more than the past thirty-five years have been focused on muscle diseases, both immunological and genetic, and for over the past 20 years, his group's research centered on Pompe disease, particularly the need to develop effective therapy for the skeletal muscle disease.

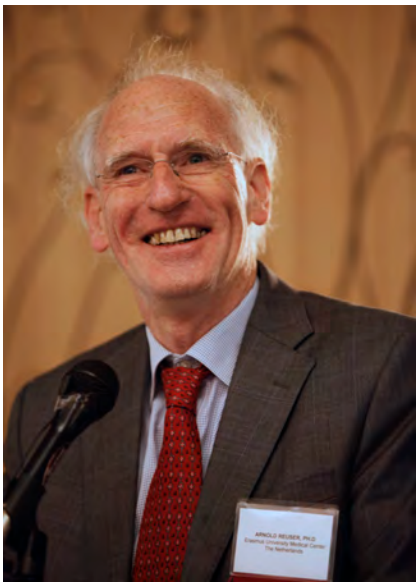
Paul Plotz came to NIH in 1965 to train in Rheumatology and to work on Immunological aspects of autoimmune diseases. This led him to an analysis of the autoimmune muscle diseases, polymyositis and dermatomyositis, and soon thereafter he was referred a patient for the treatment of "therapy-resistant myositis."

An alert medical student, Neal Boerkoel, noted that the biopsy report that was sent did not identify inflammation but did comment on the glycogen storage and mentioned the diagnostic possibility of Pompe Disease. That very night he performed an analysis of the muscle nucleic acid and identified a piece of the muscle DNA that shouldn't be there and the search was on.

The patient and her sister – both adults – had classical signs and symptoms of Pompe Disease, and Dr. Nina Raben and Dr. Neal Boerkoel and I were hooked. The group turned to Pompe Disease as the center of interest, developing animal models and studying a broad spectrum of aspects of the disease and how it might be treated.

Dr. Raben and Dr. Plotz attended the first AMDA meeting in San Antonio and almost every one since, and hosted one of the meetings at NIH. And we in the NIH group were also hooked by the House family.

Dr. Plotz remains at NIH as a Scientist Emeritus and Senior Clinician.



Dr. Arnold Reuser, Ph.D.

Dr. Reuser obtained a BSc in Chemistry and Physics followed by a MSc in Biochemistry at the University of Amsterdam. He was employed by Erasmus University Medical Center as research assistant and teacher in Cell Biology and Histology from 1973 until 1977. In 1977 he finalized his PhD thesis on "Clinical, Biochemical, and Genetic Heterogeneity in Lysosomal Storage Diseases." From 1977-1979 he worked as a Research Associate at the Institute for Cancer Research, in Fox Chase, Philadelphia, in the laboratory of Dr Beatrice Mintz where they practised stem cell technology aiming to make mouse models of human diseases.

In 1979 he returned to the Erasmus University Medical Center, and continued his research in the field of lysosomal storage diseases with a strong focus on Pompe disease.

Along the line of activities were: the characterization of acid alpha-glucosidase (GAA), its way of synthesis, glycosylation and post-translational modifications (1980-1990), the cloning of the *GAA* gene and mutation detection in patients with Pompe disease (in collaboration with Hoefsloot, Hermans and Oostra; 1987-1993), the making of a mouse model of Pompe disease in collaboration with Bijvoet and Oostra (1995-1999), and the development of enzyme replacement therapy for Pompe disease from 1984 till present in collaboration from Drs. van der Ploeg, Verbeet and Bijvoet, and the support of many others.

Marian Kroos and Marianne Hoogeveen-Westerveld provided indispensable contributions over all those years.

Arnold Reuser is at present emeritus professor Cell Biology and Genetics, and Board Member of the Pompe Center at the Erasmus University Medical Center, Rotterdam, the Netherlands. He is also a member of the Scientific Advisory Committee of the Acid Maltase Deficiency Association (USA) and IPA (International Pompe Association).

Presenter Biographies

Andrea Amalfitano, D.O., Ph.D. (Michigan State University)

Dr. Amalfitano is a board certified clinical geneticist/physician, as well a PhD trained scientist. He, along with Dr. Y.T. Chen, co-led the first-in-man study of what is now known as the drugs Myozyme and Lumizyme. He has focused much of his clinical activity and research efforts on developing viable technologies to treat human diseases, and in particular has focused his laboratory's efforts on developing a gene therapy based approach for the treatment of all Pompe patients. His laboratory first demonstrated the feasibility of using viral based gene therapy to systemically treat the affected muscles of Pompe patients, by converting the liver into an acid alpha glucosidase secreting factory. Since those initial studies his work has been confirmed in several animal models, including most recently, non-human primates, as he continues his efforts to bring this form of therapy to patient's world-wide.

Stephanie Austin, M.S., M.A. (Duke University)

Stephanie is a certified genetic counselor with a dual degree in genetic counseling and educational psychology from the University of Minnesota. She works under Dr. Priya Kishnani and her glycogen storage disease team at Duke University Medical Center. Stephanie spends the majority of her time coordinating glycogen storage disease clinical research for the Duke team. She works closely with collaborators at Duke, as well as others around the United States and internationally, to identify ways to improve the lives of people with glycogen storage disease. The Duke team has a dedication to research related to glycogen storage disease. Stephanie's research interests include the use of whole body MRI to characterize disease and the involvement of the bulbar muscles in Pompe and GSD III.

John Bach, M.D. (New Jersey Medical School)

Dr. Bach received his medical degree from the College of Medicine and Dentistry of New Jersey in 1976. He completed residency training in Physical Medicine and Rehabilitation at New York University in 1980. He was the Medical Director of the Howard Rusk Ventilator Unit at Goldwater Memorial Hospital from 1980 to 1981 and then developed a noninvasive respiratory management program at the University of Poitiers, France from 1981 to 1983. He directed the Kessler Institute ventilator unit from 1992-4. He has been on the faculty of the Rutgers New Jersey Medical School where he is a Professor of Physical Medicine and Rehabilitation, Vice Chairman of the Department of Physical Medicine and Rehabilitation, Professor of Neurosciences in the Department of Neurosciences, Director of Research and Associate Medical Director of the Department of Physical Medicine and Rehabilitation at University Hospital, Newark, N.J., Director of the Rutgers New Jersey Medical School Muscular Dystrophy Association Clinic since 1988, and Medical Director of the Center for Ventilator Management Alternatives, University Hospital, Newark, N.J. since 1992. He has over 400 peer reviewed scientific articles and book chapters and 10 medical textbooks on neuromuscular and pulmonary medicine and has lectured on these topics in 60 countries. He has received many awards for excellence in research writing, and others including the University of Medicine and Dentistry of New Jersey University Excellence Award for Patient Care, and the Newark Beth Israel Health Care Foundation Humanism in Medicine Award.

Deeksha Bali, Ph.D. (Duke University)

Dr. Bali is a professor in the Division of Medical Genetics, Department of Pediatrics and Co-Director of the Biochemical Genetics Laboratory at Duke University. Throughout her career, Dr. Bali's primary focus and passion has been the translation of laboratory science into the clinical arena, especially in the area of laboratory diagnostics and new test development for rare diseases, like glycogen storage diseases (GSDs) and lysosomal storage disorders (LSDs). With early diagnosis there is a possibility of early therapeutic intervention during the disease process like enzyme replacement therapy and small molecules intervention. Her areas of publication include various non-invasive methods for diagnosis and treatment strategies. She has been the Principle Investigator for several clinical and Research studies involving Pompe and other GSDs (GSD I, III, IV, IX). Along with the team at Duke University Medical Center, she is well recognized nationally and internationally for the contributions made to the field of Pompe disease, GSDs and other lysosomal storage diseases.

Dr. Bali has played a key role in developing CRIM status assay in Pompe disease and its correlation with underlying GAA mutations and antibody titers in clinical response to ERT. She is also a member of the North America Scientific Advisory Board for the Association of Glycogen Storage Diseases, US.

Barry Byrne, M.D., Ph.D. (University of Florida, Gainesville)

Dr. Byrne received his B.S. in 1978 from Denison University in Chemistry and his Ph.D. in Microbiology and Immunology and his M.D. from the University of Illinois in 1984. He completed his Residency in Pediatrics from the Johns Hopkins University, School of Medicine. From 1992 to 1997, Dr. Byrne held Assistant Professor appointments in Pediatrics and Pathology at Johns Hopkins University, Baltimore, MD. He was recruited to the University of Florida, Gainesville, FL in 1997. In 2002, he was appointed Professor of Pediatrics and Molecular Genetics & Microbiology and in 2002, he was appointed Director, Powell Gene Therapy Center as well as Associate Chair for Research, Department of Pediatrics. Recently, Dr. Byrne was selected as the chair of the National Institute of Health's Skeletal Muscle and Exercise Physiology Study Section on the basis of his scientific achievements and leadership abilities. He is a member of 17 Professional and Scientific Societies including The American College of Cardiology (fellow), American Society of Gene Therapy, American Heart Association and the International Society of Heart and Lung Transplantation.

Dr. Byrne is internationally recognized for his work in the areas of cardiomyopathy, transplantation and genetic therapy. His laboratory is actively involved in developing new genetic therapies for cardiovascular disease. In the area of cardiomyopathy, his lab is studying gene replacement in an autosomal recessive form of fatal cardiomyopathy in children. The disease is the prototype of lysosomal storage disorders leading to skeletal and cardiac muscle weakness. The lab has used AAV vectors to achieve sustained correction of the gene deficiency and correction of the phenotype in natural and transgenic mouse models of the disease. The current therapy is currently being proposed for human clinical trials. Similar therapies are being used to combat cardiac transplantation rejection. Secondly, the lab is investigating the ability of mesenchymal stem cells to undergo myocardial specification for the purpose of tissue repair in the heart. Finally, several projects are focused on the use of AAV vectors injected into striated muscle to achieve sustained release of therapeutic proteins, including thrombolytic factors and coagulation factors. These projects are currently funded by the National Institutes of Health (NIH), American Heart Association (AHA), and foundation grants.

Yin-Hsiu Chien, M.D., Ph.D. (National Taiwan University Hospital)

Dr. Chien holds the following positions:

1. Associate Professor, Department of Pediatrics, National Taiwan University College of Medicine, Taipei, Taiwan
2. Visiting staff, Department of Medical Genetics and Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
3. Director, Newborn Screening Center, Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan

Her Specialties include: Pediatrics, Allergy and Immunology, Medical Genetics, and Inborn Errors of Metabolism

Education:

- Doctor of Medicine, Chang Gung College of Medicine and Technology, Taoyuan, Taiwan
- Post-Graduate Studies, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine

Professor Cesare Danesino, M.D., Ph.D. (University of Pavia, Italy)

Professor Danesino received his medical degree from the University of Pavia (score of 110/110 cum laude) in 1972, and continued his training in 1973 at Mount Sinai Hospital in New York (under the guidance of Prof R. Hirschhorn). Under Dr. Hirschhorn he was trained in biochemical genetics, medical genetics, and also started working with cell cultures. Professor Danesino has worked at the University of Pavia since 1974, and is now a Full Professor of Medical Genetics.

At the University of Pavia, Professor Danesino teaches courses in Medical Genetics, Biology and Genetics to Medical students, post-graduate schools for MDs, and nursing students. He also serves as an advisor for students preparing their graduate theses. In addition, he acts as an advisor for several PhD students completing PhD-level courses in Pathology and Medical Genetics. Since 2005 he has been the Coordinator of the PhD courses in Pathology and Medical Genetics.

His scientific work has been devoted to the study of lysosomal storage diseases, prenatal diagnosis, gene dosage effect, and gene mapping. Recently he studied the parental origin of the chromosomes involved in chromosomal aneuploidies in leukemias in relation to its possible effect on the pathogenesis of these disorders.

He is responsible for a project on Rendu-Weber-Osler disease (search for mutations in ENG and ALK1 genes, genotype phenotype correlations, search for genetic polymorphism which my interfere with mutation in ENG or ALK1), and, in collaboration with the Research Hospital "IRCCS S. Matteo" in Pavia in a project to study genetic Histhiocytoses. This project (P. I. DR. M. Aricò) was funded by Telethon (project n E755). Again in collaboration with "IRCCS S. Matteo" he is involved in a project about JMML. In collaboration with IRCCS C. Mondino he is developing a project about Glycogen storage disease Type II (Pompe Disease).

Professor Danesino's clinical activity has focused on the diagnosis of genetically determined disorders, with a specific interest in Genetic Counseling. After a period of training at the Mount Sinai Hospital in New York, and further training at Istituto di Biologia Generale e Genetica Medica (1974-1976) he has been in charge of the Genetic Counseling work at the Genetica Medica, University of Pavia. From 1976-1980 he collaborated to develop the Genetic Counseling Clinic at the "Provincia di Trento" and immediately thereafter at the "Provincia di Bolzano".Since 1976 he has been in charge of Genetic Counseling work at the "Dipartimento di Patologia Umana ed Ereditaria" (University of Pavia) under agreements with the Public Health Service (ASL in Pavia) and the Research Hospital "IRCCS S. Matteo".

Professor Danesino has published over 160 papers on peer-reviewed journals; total citation number (Scopus) 2907; "H index 29.

Krystal Hayes, RN (Virginia)

Krystal is the mother of a child diagnosed with Pompe Disease. Her youngest daughter, Haley, is 9 years old and was diagnosed with infantile onset Pompe disease in 2006. She also has a 14-year-old daughter, named Britani. Krystal and her husband, David, have been married for 15 years.

For the past nine years, Krystal and her family have juggled the Pompe diagnosis while maintaining a busy lifestyle. Krystal works as a Registered Nurse and recently started her own business, where she is able to work from home. David is a history teacher and volunteer firefighter. Britani and Haley are involved in many activities and keep a busy schedule.

Over the years, Krystal has felt strongly about advocacy, awareness, and education for Pompe Disease. She began the group "Cure Pompe Disease" on Facebook with the hopes of bringing awareness to the disease and to also have a place where family and friends can connect, ask questions, and not feel alone. Krystal spoke at the FDA meeting regarding Lumizyme approval for adults and she also spoke at the Newborn Screening Advisory Committee meeting in support of the recommendation to add Pompe Disease to the Newborn Screening panel. Krystal and Haley have spoken to medical students and classes at Duke University regarding Pompe disease. Haley and her family have been ambassadors for Duke Children's Hospital for several years, assisting with fundraising efforts for the hospital.

Virginia Kimonis, M.D., MRCP (University of California-Irvine Medical Center)

Dr. Kimonis received her medical degree from Southampton Medical School, Southampton, UK. She completed residencies in pediatrics and general practice in the United Kingdom before moving to the US. She did a residency in advanced pediatrics at Massachusetts General Hospital, Boston and fellowship training in clinical and biochemical genetics at the National Institutes of Health, Johns Hopkins and Washington D.C. Children's Hospital. She is board certified in Pediatrics and Biomedical Genetics and Clinical Genetics.

Dr. Kimonis is a Clinical Geneticist-Scientist with a strong interest in the genetics of inherited neuromuscular diseases. Having identified VCP as the causal gene for inclusion-body myopathy that occur in combination with Paget disease of bone, and dementia, her lab is now focusing on translational studies. There is overlap in the clinical and molecular pathology in neuromuscular disorders such as Pompe, limb-girdle muscular dystrophy, ALS, and inclusion-body myopathy. Dr. Kimonis has also established UC Irvine as a RDRCN (Rare Diseases Clinical Research Network) site for the Natural History and treatment studies of Prader Willi syndrome.

Dr. Kimonis has established a multidisciplinary Pompe clinic at UC Irvine Medical Center with Dr. Tahseen Mozaffar as a “one-stop” clinic where patients meet with a variety of specialists at 6-month intervals to establish routine follow-up and long-term care. Through this clinic, they collect robust data for the Pompe Registry with the intention of better understanding the natural history of the disease and also responses to a variety of novel treatments.

Priya Kishnani, M.D. (Duke University Medical Center)

Dr. Kishnani is Chief of the Division of Medical Genetics, Department of Pediatrics and Director of the YT and Alice Chen Center for Genomic Research, which has a focus on developing new therapies for rare genetic disorders. She holds certification from the American Board of Medical Genetics and the American Board of Biochemical Genetics.

Throughout her career, Dr. Kishnani’s primary focus has been the translation of laboratory science into the clinical arena, especially in the area of such therapeutic interventions as enzyme replacement therapy and small molecules.

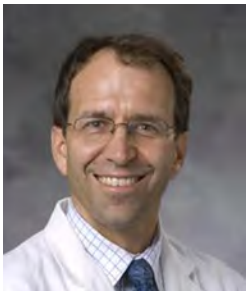
She has a long-standing research and clinical interest in Pompe disease, and has been the Principle Investigator for several clinical trials involving Pompe disease. She was the lead investigator for the pivotal trials of Pompe disease, which led to FDA approval of Myozyme™ as the first treatment for Pompe disease in 2006. Her team at Duke University Medical Center is well recognized internationally for the contributions made to the field of Pompe disease.

Dr. Kishnani remains active in investigating the natural history of Pompe disease and has been instrumental in uncovering several long-term complications, including speech and swallowing dysfunction, pulmonary issues, lingual weakness, cardiac arrhythmias, vascular involvement, urinary and bowel incontinence, sleep and gait disturbances, small fiber neuropathy, and other issues in Pompe disease. She has played a pivotal role in identifying prognostic factors such as role of CRIM status, antibody titers and alternative dosing strategies in clinical response to ERT. Biomarker development such as urine hex 4, whole body MRI, investigating treatment strategies for the immune responses to therapeutic proteins, ways to enhance enzyme delivery to skeletal muscle and CNS are areas of research interest for her.

She and the Duke team played an integral role in the nomination and approval for the addition of Pompe disease to the RUSP (Recommended Uniform Screening Panel) for newborn screening in the US. She is Chair of the North American Pompe Registry Board and is a member of the International Pompe Registry Board of Advisors. Dr. Kishnani is Chair of the Scientific Advisory Board for Association of Glycogen Storage Diseases, US. She is a task force member for PCORnet for the rare disease initiative.

Dr. Kishnani has received several awards, including “Exceptional Parent Maxwell J. Schleiffer Distinguished Service Award,” for passion, dedication, professionalism and inspiration to people with disabilities, particularly those with Pompe Disease,” the “Ruth and A. Morris Williams, Jr. Faculty Research Prize,” for intellectual vigor, dedication, and scientific ingenuity needed to make a critical impact on the future of medical research.

Dr. Kishnani is the proud mother of two wonderful children, Kunal, 21 and Sujata, 18. She would be unable to succeed in her work without the love and support of her husband, Sunil.



Dwight Koeberl, M.D., Ph.D. (Duke University Medical Center)

Dr. Koeberl attended Mayo Medical School and Graduate School, before moving to UCSF for his pediatrics residency. He then completed fellowship training in Clinical and Biochemical Genetics at the University of Washington, before joining the Division of Medical Genetics in the Department of Pediatrics at Duke University in 1999. At Duke he has focused upon the development of new therapies for glycogen storage diseases. He serves as Medical Director for the Pediatrics Biochemical Genetics Laboratory and sees patients in the Metabolic Clinic. He will discuss preclinical development of gene therapy for Pompe disease at this Conference.

Professor Giancarlo Parenti, M.D. (Federico II University, Naples)

Professor Parenti earned his medical degree in 1980 from Federico II University, Naples. He also completed a Residency in Pediatrics (1981-84) at Federico II University, Naples.

Research training

- 1979-1985 and 1987-1989: Department of Pediatrics, Federico II University, Naples (laboratory directed by Prof. Generoso Andria).
- 1985-1986: Department of Cell Biology and Genetics, Erasmus University, Rotterdam, the Netherlands (directed by Prof. Hans Galjaard).
- September-December 1991 and July-November 1994: Institute of Medical Genetics, Baylor College of Medicine, Houston, Texas, USA (laboratory directed by Prof. Andrea Ballabio).

Dr Parenti is a member of SISMME (Italian Society for the Study of Inherited Metabolic Diseases), of the SSIEM (Society for the Study of the of Inborn Errors of Metabolism), and of the Italian Society of Pediatrics. From 2002 to 2005 he has been a member of the council of SISMME, and corresponding member of SSIEM for Italy. He is currently an Associate Professor in the Department of Pediatrics at Federico II University in Naples, and an Associate Investigator for Telethon Institute of Genetics and Medicine.

In the field of Pompe Disease, Prof. Parenti's interests are: molecular characterization of patients; evaluation of the effects of enzyme replacement therapy; enhancement lysosomal exocytosis by TFEB overexpression; analysis of microRNA profile and identification of markers of disease; development of pharmacological chaperone therapy; and synergy between pharmacological chaperones and enzyme replacement.

Prof. Parenti was the recipient of several research grants, from different agencies including Telethon Foundation Ministero dell'Università e Ricerca (MIUR), AIFA, Acid Maltase Deficiency Association (AMDA), etc.

Nita Patel, R.N. (Amicus Therapeutics)

Nita is a registered nurse with years of experience in clinical research, obstetrics and genetic nursing. She has been working at Amicus since September 2011. Her past experience involved managing a lysosomal treatment center at St. Peter's University Hospital located in New Brunswick, NJ. Nita has managed patients with Fabry, Gaucher, Pompe and MPS, her passion is to advocate for patients and bring their needs to industry and drug development. Nita has been an Ambassador for Needy Meds since 2012; she continues to help patients with their needs to access the medical care they deserve.

Pim Pijnappel, Ph.D. (Erasmus University, the Netherlands)

Dr. W.W.M. Pim Pijnappel is a molecular stem cell biologist. Previous research was performed on genetic engineering of stem cells, basic mechanisms of gene expression (1, 2) and cellular reprogramming to stem cells (3). Since 2012, Dr. Pijnappel heads the Molecular Stem Cell Biology group of the Center for Lysosomal and Metabolic Diseases (CLMD) of the Erasmus MC in Rotterdam. Through basic and applied research, the laboratory aims to expand options for the diagnosis (4) and treatment of patients with a lysosomal storage disorder with a focus on Pompe disease. Dr. Pijnappel participates indirectly in patient care, for instance through the development of new diagnostic procedures, the monitoring of antibody formation during enzyme replacement therapy, and the interpretation of laboratory outcome measures. In this role, the laboratory also advises on diagnostic procedures, and translates the finding of genetic defects into functional deficiencies (genotype-phenotype correlations). The role of stem cells and the exploration of advanced methods for gene therapy are major research topics.

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(4.) Bergsma, AJ, Kroos M., Hoogeveen-Westerveld, M, Halley, D., van der Ploeg AT., Pijnappel, W.W. Hum Mutat, 2015 Jan;36(1):57-68. See video highlight.

Suyash Prasad, M.D. (Audentes Therapeutics)

Dr. Prasad is a Pediatrician, Clinical Development Physician and Translational Scientist, with a wide range of experience in medicines development for infants and children with rare and severe diseases. He is currently based in San Francisco in the role of Senior Vice President and Chief Medical Officer at Audentes Therapeutics, which is an organization that is dedicated to developing gene therapy approaches for treating infants and children with diseases that have no alternative options.

Suyash graduated in Medicine at the University of Newcastle-upon-Tyne, UK, where he received commendations for Pediatrics, Obstetrics and Gynecology, and Medical Ethics. His Pediatric training was completed at recognized centers of excellence in the UK and Australia before he moved to industry. He is a United Kingdom board certified physician and is a member of the Royal College of Physicians (MRCP), the Royal College of Padiatrics and Child Health (MRCPCH), and a Fellow of the Faculty of Pharmaceutical Medicine (FFPM). Suyash has published in several scientific journals on aspects of Pediatric medicines development and is a past recipient of the Outstanding Contribution Award from the Faculty of Pharmaceutical Medicine of the UK Royal College of Physicians.

Nina Raben, M.D., Ph.D. (National Institute of Health)

Nina Raben was born in Moscow, Russia (the former Soviet Union). She received her medical degree from the Moscow Medical Institute, and her Ph.D degree in Biochemistry from the Academy of Medical Science, Moscow. She joined NIDDK in 1987, and since 1990 has been working on inflammatory and metabolic myopathies at the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the NIH. The major focus of her research is a genetic disorder caused by a deficiency of lysosomal enzyme acid alpha-glucosidase, known as glycogen storage disease type II or Pompe disease. The studies include mutational analysis of the gene and development of several knockout and transgenic mouse models of Pompe disease, pre-clinical studies with recombinant human enzyme and investigation of the role of autophagy in the pathogenesis of the disease, and identification of transcription factors EB and E3 as potential therapeutic targets in Pompe disease.

Professor Benedikt Schoser, M.D. Ph.D. (Friedrich-Baur-Institute)

Professor Schoser has 20 years experience as a neurologist and myopathologist in a variety of areas of neuromuscular disorders, including myopathological, structural, biochemical and molecular genetic muscle research, and clinical trials. The major focus of his research activities is the genetic-pathomorphological base of neuromuscular disorders, like limb girdle muscular dystrophies and especially myotonic dystrophies. To establish the analysis of pathogenesis, he collected multiple tissue samples including human myoblasts and DNA, of glycogen storage diseases incl. GSDs patients during the past 15 years.

After medical school at the University of Mainz, Germany from 1985-1993, he finished his medical thesis (Dr. med.) at the Department of Neuropathology, University of Mainz in 1993. He was a resident and faculty member in Neurology and Psychiatry at the University Clinics of Mainz, Frankfurt and Hamburg, Germany. In 2000 he joined Professor Thomas Jentsch for his postdoctoral fellowship at the Department of Neuropathophysiology, Zentrum für Molekulare Neurobiology Hamburg, Germany.

In 2001 he moved to the Friedrich-Baur-Institute at the Department of Neurology, Ludwig-Maximilians-University of Munich. In 2000 he was board certificated in Neurology, and in 2001 board certificated as Intensive Care Neurologist. In 2005 he got the board certification as a neurophysiologist. Since 2004 he is senior consultant neurologist and finished his faculty rank (habilitation) in Neurology in the same year. In 2006 he was visiting professor at the Baylor College in Houston, USA. Since 2010 he is associated Professor of Neurology and head of the Interdisciplinary Center for Neuromuscular Disorders, LMU Munich.

Professor Schoser has served on numerous peer review committees of the Italian Telethon, French AFM, and British MDC reviewing international grant applications in neuromuscular disorders. He is adhoc-reviewer for several international journals, incl. Brain, Annals of Neurology, Neurology, Journal of Neurology, American Journal of Human Genetics, European Journal of Human Genetics, Neuromuscular disorders, and has co-authored more than 150 peer-reviewed publications (25 in the field glycogen storage diseases) in clinical and translational science. Since 2003 he is member of the German network of muscular dystrophies (MD-Net), and since 2009 he is member of the DFG-research unit FOR 1228 “Molecular pathogenesis of myofibrillar myopathies”. Since 2013 he is member of “OPTIMISTIC”, a 7thEU framework funded clinical trail in DM1. In 2013 he organized the international glycogen storage disease conference in Heidelberg, Germany with 345 participants from 38 countries. Since March 2015 he is the first elected chair of the new funded European Pompe Consortium EPOC.

Barbara Smith, Ph.D., PT (University of Florida, Gainesville)

Dr. Smith completed her master’s degree in physical therapy at University of Pittsburgh and earned a PhD in Rehabilitation Science at University of Florida. She is a member of University of Florida's Child Health Research Research Institute and evaluates ventilatory function of patients in the University of Florida's interdisciplinary Neuromuscular Clinic. Her research focuses on the control of breathing in conditions of health and neuromuscular disease, and on harnessing combined rehabilitation and regenerative treatment approaches, including exercise training, diaphragm pacing, and gene therapy, to restore ventilation in neuromuscular disease.

Susan Sparks, M.D., Ph.D. (Genzyme Corporation)

Susan Sparks joined the Genzyme, a Sanofi company, US Medical Affairs team as a Medical Director, Genetic Diseases focusing on Pompe disease in December of 2014.

She is a board certified Clinical and Clinical Biochemical Geneticist with 10 years of clinical experience. In her previous positions at Children’s National Medical Center in Washington, DC and Levine Children’s Hospital/Carolinas Healthcare System in Charlotte, NC, she combined clinical practice in genetics, metabolism and neurogenetics together with an active translational and clinical research program in muscular dystrophies.

Hannerieke van den Hout, M.D., Ph.D. (Erasmus University Medical Center, the Netherlands)

Dr. van den Hout obtained her degree in Medicine at the Maastricht University in the Netherlands in 1995. She wrote her PhD thesis on the first treatment world-wide of 4 patients with classic infantile Pompe disease with recombinant alpha-glucosidase from rabbit milk in Rotterdam. Following her training in paediatrics and child neurology, she specialized as a Paediatric Neurologist in neurometabolic and neuromuscular diseases. She is currently working as a Paediatric Neurologist and Clinical Supervisor at the Center for Lysosomal and Metabolic Diseases with Professor Ans van der Ploeg at the Erasmus MC-Sophia Children's Hospital in Rotterdam.

Dr. van den Hout's main research interest focuses on the field of lysosomal disorders. She has authored and co-authored various publications in peer-reviewed journals.

Chris van der Meijden, M.D. (Erasmus University Medical Center, the Netherlands)

Chris van der Meijden (1986) studied medicine at the Erasmus University Rotterdam, the Netherlands. After finishing medical school in 2011, he worked as a junior house officer at the Albert Schweitzer hospital in Dordrecht. Since March 2013 he works as a research physician at the Center for Lysosomal and Metabolic diseases at the Erasmus University Medical Center Rotterdam. Here he performs clinical research on patients with the non-classic form of Pompe disease and manages the IPA/ Erasmus MC Pompe survey.

Professor Ans van der Ploeg, M.D., Ph.D. (Erasmus University Medical Center, the Netherlands)

Prof. van der Ploeg is head of the subdivision of Metabolic Diseases and Genetics at the department of Pediatrics and Chairman of the Center for Lysosomal and Metabolic Diseases, a joined initiative of the departments of Pediatrics, (Child) Neurology, Internal Medicine, Clinical Genetics and Hospital Pharmacy to improve treatment, care and diagnosis of children and adults, to stimulate translational research and to provide education and to disseminate information.

In 2001 she joined the Department of Metabolic Diseases and Genetics. From 1994-2001 she was Staff Member on the ICU of the department of Neonatology at the Sophia Children's Hospital. She completed a residency in Pediatrics in 1994.

Professor van der Ploeg received her MD cum laude in 1985 at the Erasmus University. Since 1985 she has been involved in research on Pompe disease and development of enzyme replacement therapy. From 1985 till 1989 she worked in the laboratory of the Department of Clinical Genetics on her PhD. The title of her thesis was "Glycogenosis type II: A study on clinical heterogeneity and enzyme replacement therapy." Since then she has published more than 100 articles on Pompe disease and has given many lectures at scientific meetings on this subject. She received awards for her work on the development of enzyme therapy for Pompe disease in 1991, 1997 and 2009. She acts as a medical advisor for various patient organizations in the Netherlands and in other countries.

Wouter Vervecken, MsC, Ph.D. (Oxyrane)

Dr. Vervecken is the Chief Technology Officer at Oxyrane, a biotech company focused on developing Enzyme Replacement Therapies for Lysosomal Storage Diseases, based on a proprietary glyco-engineered yeast expression platform. Prior to joining the company in 2008 he was a post-doctoral researcher at VIB & Ghent University, Ghent, Belgium in the labs of Prof. Contreras and Prof. Callewaert, where his research was focused on metabolic engineering of microbial glycosylation. Wouter Vervecken holds a MSc and a PhD in biotechnology.

Liron Walsh, M.D. (Biomarin)

Dr. Liron Walsh joined BioMarin in April 2015 and serves as a Medical Director and Lead Clinical Scientist for product in development - Pompe disease (Phase I, II, III).

Previously he served as Clinical Research Medical Monitor at Amgen. As Lead Clinical Scientist his oversight included drug safety and phase III clinical studies in the development of secondary hyperparathyroidism treatment in adults and children with chronic kidney disease. In addition to successfully completing two Phase-III clinical studies, Dr. Walsh led the program's pediatric program and Japanese partnership.

From 2010 to 2011 Dr. Walsh served as Hospitalist Medicine Program Director at Newark Beth Israel in Newark, NJ. He is board certified in both internal medicine and nephrology, having earned his Fellowship in nephrology/transplantation from Mount Sinai School of Medicine in 2010.

Dr. Walsh received an M.D. degree from the University of Toronto in 2004. In his free time, Dr. Walsh likes to spend time with his wife and two children. He also enjoys the outdoors, travelling and music.

Abstracts

The Natural History of Pompe Disease

Hannerieke van den Hout, M.D., Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

In 1932 Johannes Cassianus Pompe (1901-1945) reported a 7-month old girl, who had succumbed to extreme hypertrophy of the heart. Microscopic analysis showed accumulation of glycogen not only in the heart, but also in the liver, kidneys and skeletal muscles. This was the first report of Pompe disease. In the last 25 years, cloning of the gene has led to the production of recombinant human alpha-glucosidase in CHO-cells and in the milk of transgenic mice and rabbits and the start of the first clinical trial. With treatment available now, we can barely remember how the disease was without treatment. However to enable us to carefully appreciate the effect of treatment we need to know where we are coming from.

The disease presents as a spectrum of phenotypes, ranging from a rapidly fatal phenotype in infants (the "classic infantile" form) to slower progressive phenotypes in older children and adults (the "late-onset" form). In classic infantile Pompe disease – with virtually absent lysosomal alpha-glucosidase activity – massive glycogen storage leads to progressive destruction of skeletal and cardiac muscle, resulting in severe hypotonia, preventing the achievement of any motor milestones, a progressive hypertrophic cardiomyopathy, and death within 6-8 months. The late-onset phenotype, which affects both children and adults, is dominated by a slowly progressive limb-girdle myopathy leading to gradual loss of ambulation. Involvement of respiratory muscles limits their average life-span, while the heart is usually not affected. While late-onset Pompe disease is typically distributed in a limb-girdle pattern, many patients have unfamiliar features such as ptosis, bulbar weakness and scapular winging.

In this presentation the natural course of Pompe disease will be presented including non-muscular symptoms.

Ten years of the International Pompe Survey: Patient Reported Outcomes Provide Insight into the Natural Course and Effects of Treatment

Chris van der Meijden, M.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

The IPA/Erasmus MC survey is an international survey that collects information from Pompe patients from a number of countries. It is a collaboration between Erasmus MC University Medical Center and the International Pompe Association (IPA). Each year, patients are asked to provide information on their symptoms and problems related to the disease, as well as on fatigue, participation and quality of life. The survey was established in 2002 to collect information on the natural course of Pompe disease and its burden on patients. It was also set up to investigate the effects of ERT once this became available.

In this presentation we will review our results of following patients for more than 10 years, discuss the survey's contribution to the field of Pompe research, and discuss the importance of patient reported outcome measures.

The continuous contributions of many patients for over a decade have made the Pompe survey into one of the largest databases in existence, furthering the understanding of Pompe disease and its treatment.

Report from Genzyme's Pompe Registry

Virginia Kimonis, M.D.
University of California-Irvine Medical Center

The Pompe Registry is a multi-center, international, observational program for patients with Pompe disease that was established in 2004 to track the natural history and outcomes of patients through routine clinical practice. Demographic data gathered over 10 years by this registry on 1292 patients in 34 countries across the globe indicates that the majority (1,020 or 78.9%) of patients had late-onset Pompe disease (LOPD) with onset >12 months or ≤12 months without cardiomyopathy, and 178 (13.8%) had infantile-onset (IOPD) with onset ≤12 months with cardiomyopathy.

Symptom onset and the mean age of diagnosis were 2.9 and 4 months respectively for IOPD and 26.5 and 33.5 years for LOPD respectively. On reviewing the clinical features in IOPD patients, hypotonia was reported in 94.7%, proximal weakness in lower extremities in 88.5%, and upper extremities in 80.5%, joint contractures in 23.6% and scoliosis in 13.8% of patients. In LOPD patients, hypotonia was reported in 42.8%, proximal weakness in lower extremities in 94%, and upper extremities 78%, joint contractures in 11.8% of patients and scoliosis in 35.8 %. Ambulation was impaired in 55.8% IOPD and 78.4% of LOPD patients. Two-thirds (67.6%) of LOPD patients reported to have lost ambulatory capabilities, and 48.8% reported using ambulation devices in contrast to 5% and 25.3% in the IPD group respectively. Overall, 47.1% of patients were receiving respiratory support, 43.7% of classic IOPD patients and 48.7% of LOPD patients with the latter group more likely to have non-invasive ventilatory support. On reviewing the method of diagnosis, an increased use of both enzyme and DNA diagnosis was reported, the latter doubling from 23% to 54.2%. In this 10-year cohort, 82.4% of patients were reported to have been treated with enzyme; the mean age of starting infusions in these groups were 7.3 and 39.5 years respectively.

Overall the registry has been very helpful in obtaining natural history data in Pompe disease in patients and will help identify areas of unmet needs. The impact of the registry on a multidisciplinary Pompe clinic at UC Irvine Medical Center will be discussed,

Various Diagnostic Approaches and Genetic Counseling Issues in Pompe Disease

Deeksha Bali, Ph.D. and Stephanie Austin, M.S., M.A.
Duke University Medical Center

With Pompe disease being recently added to the Recommended Uniform Screening Panel of Diseases for Newborn Screening in the United States (March 2015), many states are embarking on newborn screening for Pompe disease. However, many diagnostic questions are emerging and still remain unanswered, especially for patients with novel variants of unknown significance (VOUS), patients with pseudo-deficiency alleles with single mutations, and patients suspected to have late onset Pompe disease. The focus of this presentation is to briefly discuss different diagnostic approaches for the accurate diagnosis of complicated cases of Pompe disease using acid alpha glucosidase (GAA) enzyme testing in dried blood spots, blood leukocyte, muscle biopsy, and skin fibroblasts and the utility of urine Hex4 testing and GAA mutation analysis. We will also provide an overview of genetic counseling for Pompe disease, including a discussion of carrier screening and testing family members of a patient with Pompe disease.

Patient Management & Current Standard of Care

Priya Kishnani, M.D.
Duke University Medical Center

Management guidelines for patients with Pompe disease across the disease spectrum have been published for various parts of the world. The management of Pompe disease requires a comprehensive multi-disciplinary approach encompassing strategies that include appropriate and timely interventions that are disease-specific to target the underlying disease process and symptom-specific manifestations. Clinical experience with treating and managing the disease is important. Care is a collaboration across multiple specialties and can include specialists in inherited metabolic diseases, developmental pediatrics, cardiology, pulmonology, neurology, anesthesiology, urology, and immunology. Patients will often require physical, occupational, and speech therapy, and should be evaluated early for these needs. Appropriate intake of calories for patients is important, and input from a dietician with experience in nutritional counseling of patients with Pompe disease therefore is recommended. Genetic counseling is needed for new families. Overall coordination of care across disciplines and continued oversight of the care and management by a clinician experienced in treating patients and knowledgeable about the disease itself, potential complications, and the nuances of treatment are essential. Most importantly, the treatment of any patient with Pompe disease, as with other inherited metabolic diseases, needs to be tailored to the individual patient. These aspects will be discussed during my talk.

Respiratory Management of Pompe Disease (Acid Maltase Deficiency)

John Bach, M.D.
New Jersey Medical School

Episodes of respiratory failure can be avoided for people with acid maltase deficiency by using inspiratory and expiratory muscle aids to maintain normal breathing volumes and effective cough flows. Because throat muscles are generally stronger than skeletal muscles, people with AMD virtually never need tracheostomy tubes because even severely affected children with AMD can use up to continuous noninvasive ventilatory support without them. People intubated for general anesthesia for surgical interventions or intubated because of pneumonia and respiratory failure can always be extubated to noninvasive respiratory muscle aids without resort to tracheostomy.

Diaphragm Pacing in Pompe Disease: 2015 Update

Barbara Smith, Ph.D., PT
University of Florida-Gainesville

This presentation reviews neuromuscular contributions to chronic ventilatory insufficiency in Pompe disease, and discusses the rationale and indications for using a diaphragm pacemaker to support ventilator-free breathing. We will examine post-operative approaches to using pacers to facilitate diaphragm conditioning and ventilator weaning. Functional results from patients to date will be presented, as well as the implications of these findings for future work.

Exercise Presentation in Pompe

Ans van der Ploeg, M.D., Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

Pompe disease presents as a wide clinical spectrum, the most prominent symptoms in adults being proximal skeletal muscle weakness and respiratory problems. Enzyme replacement therapy (ERT) has been shown to elicit positive effects, but patients' fitness and physical functioning may be further supported by treatments additional to ERT, such as exercise training and respiratory muscle training.

In 2011 a training study was started in the Erasmus Medical Center, Rotterdam, the Netherlands, investigating whether exercise training is a safe and useful adjuvant therapy for adult Pompe patients receiving enzyme replacement therapy. 25 mildly affected patients were given 36 sessions of standardized aerobic, resistance and core stability exercises over 12 weeks. This study showed that this combined training program is safe and improves endurance, core stability, pain and fatigue in patients.

In this presentation we will present the results of this training study and review the existing studies on respiratory muscle training. We will use this information to give recommendations for training of Pompe patients, including more severely affected patients.

Parent Perspective: Living a "Normal" Pompe life

Krystal Hayes, RN
Bracey, Virginia

When Krystal and her family received the initial diagnosis of Pompe Disease for their 6-month old daughter, Haley, they were naturally devastated and overwhelmed. For the last 9 years, they have strived to provide a "normal" childhood for Haley and her older sister, Britani. Krystal's presentation is about how they have taken a serious diagnosis and "turned lemons into lemonade" or "Pompe disease into a Normal life" and other tips along the way. Krystal hopes you can take something from it and live life to its fullest, no matter the given circumstances.

Long-term Expression and High Level Secretion of Acid α-Glucosidase from the Livers of Non-Human Primates can be Achieved Safely with Adenoviral Gene-Therapy

Andrea Amalfitano, D.O., Ph.D.
Michigan State University

Pompe disease is a lysosomal storage disorder that can result in progressive weakness, cardiomegaly, respiratory insufficiency, and death due to genetic insufficiency of acid α-glucosidase (GAA), and abnormal accumulation of glycogen in multiple muscle tissues. Like other lysosomal storage disorders, achieving a sufficient plasma concentration of the deficient enzyme can prolong the life of patients with Pompe disease, due to uptake of precursor GAA by cardiac and skeletal muscle cells, and as a result, decreases in muscle glycogen storage. For this reason, we originally developed a liver-directed gene therapy approach for Pompe patients, with the goal being high-level liver secretion of GAA sufficient enough to sustain for long periods of time a critical plasma GAA level. Furthermore, the plasma levels of liver secreted GAA would be sufficient to allow for uptake by the multiple muscle tissues affected by Pompe disease. We have previously demonstrated that in mice, liver transduction using a helper-dependent adenovirus expressing GAA (HD-Ad/GAA) was capable of allowing the liver to secrete large amounts of the precursor form of recombinant GAA into the blood stream for extended periods of time, and this resulted in cardiac and skeletal muscle uptake of the liver secreted GAA. After validating our vector in mice, we used a balloon-catheter occlusion method to safely administer HD-Ad/baboon GAA (HD-Ad/bGAA) into the liver of baboons. The animals tolerated the procedure well, and we confirmed that the liver of non human primates can secrete high levels of GAA for at least 6 months after a single injection with the adenovirus based GAA vector. We furthermore detected active GAA in the heart and skeletal muscles of the treated animals, and observed no immune response against the enzyme. This work validates our proof of concept studies in mice, and justifies further studies of liver directed gene therapy using Adenovirus based vectors for potential future use in patients affected by all forms of Pompe disease.

Gene Therapy

Barry Byrne, M.D., Ph.D.
University of Florida-Gainesville

Pompe disease results from a deficiency or absence of the lysosomal enzyme acid alpha glucosidase (GAA), resulting in lysosomal glycogen accumulation that impacts striated muscle and the CNS, including activation of the neuromuscular junction (NMJ). Respiratory failure is the leading cause of morbidity and mortality in Pompe patients. AAV vectors expressing GAA have been evaluated in a phase I/II study in ventilator-dependent and independent pediatric Pompe patients. These studies are based on the finding that accumulation of glycogen in spinal motor neurons contributes to weakness and diaphragmatic dysfunction observed in Pompe disease. In a number of preclinical studies, we have found that restoration of GAA activity in muscle and neural tissue is able to reverse ventilatory insufficiency by reversing motor neuron dysfunction and restoring the integrity of the NMJ. The principle defect in the motor unit is related to deficiency of NMJ structure and function. New evidence also indicates the need for early intervention related to neural dysfunction since motor neurons show evidence of apoptosis in the murine model of Pompe. These deficits are present early in the mouse model and restoration of GAA activity in the muscle and neurons before 6 months of age leads to restoration of in situ force production. After 18 months of age, the loss in motor neurons leads to permanent deficits in force production of the tibialis anterior. A clinical trial of AAV1-mediated restoration of GAA activity in the diaphragm and phrenic motor neurons has been conducted. Nine subjects have been enrolled in the study and all subjects have undergone one year of follow up. There were no adverse events related to the study agent. All children had improvement in spontaneous ventilatory endurance from baseline to the one-year study endpoint. Additionally, findings related to immune management pave the way for future clinical studies in adults and younger subjects who are candidates for systemic administration of the study agent. We conclude that a complex motor program leads to phrenic motor dysfunction in Pompe disease. The loss of neuromuscular junction formation is a major contributor of weakness and ventilatory failure and these deficits can be prevented by early administration of AAV-GAA, which leads to rescue of the CNS defecits. Future studies will utilize the AAV9-derived GAA to lead to more efficient targeting of muscle and motor neurons following systemic vector delivery.

Gene Therapy

Dwight Koeberl, M.D., Ph.D.
Duke University Medical Center

The development of gene therapy has advanced to a point where a cure for Pompe disease can be foreseen. Pompe disease (glycogen storage disease type II; acid maltase deficiency) is a devastating myopathy resulting from acid a-glucosidase (GAA) deficiency in striated and smooth muscle. Despite the availability of enzyme replacement therapy (ERT) with recombinant human (rh) GAA, many patients have poor outcomes including mortality due to clinically significant anti-GAA antibody responses. The limitations of ERT have prompted the preclinical development of gene therapy for Pompe disease. Clinical trials of efficacious gene therapy will greatly advance treatment for Pompe disease by correction GAA deficiency and suppressing immune responses against rhGAA.

Gene Therapy in Human Diseases: Recent Advances

Pim Pijnappel, Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

Gene therapy is the delivery of a gene to cells or tissues with the aim to alleviate the symptoms of a particular human disease. A major challenge is how to deliver the gene to the patient in a safe yet efficient manner. Two strategies for gene delivery are currently tested in a variety of human disorders in preclinical or clinical settings: those using adenovirus-associated virus (AAV) or lentivirus (LV). Each method has its own advantages and challenges. AAV-mediated gene therapy is relatively safe as it does not alter the human genome. The challenges are to achieve long-term and stable high expression of the desired gene without provoking an immunological response. Lentiviruses integrate into the host genome and can provide long-term stable gene expression levels. LV-mediated gene therapy experienced a drawback with previous lentiviral backbones that proved unsafe when tested in clinical trials. However, new-generation lentiviral backbones have an improved safety profile and ongoing clinical trials including those with Wiskott-Aldrich and Metachromatic Leukodystrophy patients have shown to be safe up to date. Previous work using a mouse model for Pompe disease showed that a lentiviral gene therapy approach using hematopoietic stem cells can successfully counteract the disease[1]. Future work should focus on the further development of this approach to enable a possible clinical implementation.

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ERT: What Have We Learned So Far Roundtable

Yin-Hsiu Chien, M.D., Ph.D.
National Taiwan University Hospital, Taipei, Taiwan

Enzyme replacement therapy (ERT) is now the standard treatment for Pompe disease. However, in order to have the best therapy outcomes, it is necessary to make the diagnosis early. National Taiwan University Hospital's (NTUH) newborn screening center, lead by Dr Paul Wuh-Liang Hwu, has been conducting the first population newborn screening for Pompe disease since 2005. We demonstrated that newborn screening coupled immediately with ERT provides the best outcome for classic infantile-onset Pompe disease, but residual muscle weakness and other morbidity promotes development of second-generation therapies for improvements in both the muscular and neurologic aspects. For later-onset Pompe disease (including atypical infantile), we currently monitor their manifestations regularly and initiate ERT only if symptomatic. Further research is warranted to decide ERT initiation time for those individuals especially with newly discovered genotypes.

ERT: What Have We Learned So Far Roundtable

Priya Kishnani, M.D.
Duke University Medical Center

Enzyme replacement therapy (ERT) with alglucosidase alfa for Pompe disease (PD) has improved survival in infantile cases and improved quality of life and disease stabilization in late onset cases. We will describe clinical outcomes, emerging issues and the role of increased dose of ERT in infantile PD. The long term experience of our Center with immune modulation will be provided. .

We will also discuss emerging issues in late onset cases, including the systemic manifestations of the disease and the role of respiratory muscle strength training, role of beta agonists and other supportive care.

The journey of getting Pompe disease added as a core condition to the Recommended Uniform Screening Panel for state newborn screening (NBS) in the US and its implications will be shared.

I will talk about Pompe patient population we follow at Duke University, our recommendations for start and stop of ERT, and other aspects of care.

ERT: What Have We Learned So Far Roundtable

Benedikt Schoser, M.D., Ph.D.
Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Germany

Benedikt Schoser works as a neurologist and myopathologist in the rank of a Professor of Neurology at the Friedrich-Baur-Institute (FBI) at the Department of Neurology, Ludwig-Maximilians-University of Munich. The FBI is one of the major referral centers for neuromuscular disorders in Germany.

The first Pompe patient at the FBI was diagnosed in 1974 by a muscle biopsy. Since 1974 in total 97 Pompe patients of all ages have been diagnosed; 47 within the last decade. We started administering ERT on a regular base in 2006. At the FBI we see 26 adults on a regular base, and 12 patients are infused every 2nd week. Two kids are having their infusions at Wolfgang Müller-Felber´ Neuropaediatrics department.

I will talk about our Pompe patient population, and our recommendations for start and stop of ERT, which are in line with the American recommendations. Furthermore, I will talk about the newly founded European Pompe consortium EPOC.

ERT: What Have We Learned So Far Roundtable

Ans van der Ploeg, M.D., Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

And: Where should we go from here? We have come a long way, but the quest for the ultimate treatment has not ended yet. We continuously need to strive as pioneers for a better future of our patients. That is what drives me.

My personal experience: Pompe disease has become part of my life since 1985 when I decided to perform my 4 years thesis in the laboratory with Arnold Reuser on the development of enzyme replacement therapy. At that time I did not realize that this was a life-time decision. It started with purification of alpha-glucosidase from natural sources and experiments on muscle cells of patients to clear glycogen from patient cells. Although the experiments were successful, it also became evident that production from natural sources never would be sufficient to treat all patients. The next steps we made in the lab were cloning of the gene and generation of a knock-out mouse for Pompe disease. These important steps opened the way to demonstrating the efficacy of enzyme replacement therapy in animal models; and large-scale production of recombinant human alpha-glucosidase for human use. The ultimate moment came in 1999 when we treated the first infantile patient worldwide with recombinant human alpha-glucosidase. The most rewarding moment was when the patients survived and achieved previously unmet milestones, such as walking. Now 16 years later three of the four infantile patients from this first trial are still alive, as are the three childhood onset patients that participated. The first "infants" will soon become adults.

The Pompe Center/Center for Lysosomal and Metabolic Diseases, Rotterdam, the Netherlands: Since the first application of ERT our center has been involved in various clinical trials among which the Multicenter Placebo Controlled Late Onset Treatment Study, which included 90 children and adults with Pompe disease. After approval of enzyme therapy in 2006 the Venter became the national referral center for Pompe disease. The center covers the multidisciplinary care of infants, children and adults with Pompe disease. Doctors with different medical specialties, pharmacists, paramedics and basic researchers work closely together. Over the years the Center has evaluated close to 200 patients, which are all the patients from the Netherlands and patients from various other countries including the US. Before ERT is initiated patients are evaluated by a multidisciplinary team, which decides whether ERT is indicated. Patients start their therapy in hospital. The majority of the patients are transitioned to home-based therapy at a later stage. Currently more than 80% of our patients receive ERT at home. Nurses specialized in home-based therapy supervise the home based therapies. These nurses are trained and educated by the center.

Effects of ERT and monitoring: Since the introduction of ERT it has become evident that ERT has a positive effect on many outcome measures in infants, older children and adults. Positive effects were observed on survival, mobility (distance walked), pulmonary function, fatigue, quality of life and other parameters. Unfortunately, not all patients respond equally well. Monitoring of patients via standardized follow-up protocols, including patient reported outcome remains extremely important. We use these protocols also to study effects of supportive programs such as training; alternative dosing regimens or immunomodulation.

How to move on: Knowledge of tomorrow is more than today. Combining the continuous efforts towards a better understanding of the natural course and the effects therapy; of the complex mechanisms involved (such as autophagy and muscle regeneration and repair), the role of antibodies and dosing advances the prospects for patients. At the same time we need to invest in the development of innovative therapeutic strategies such as gene and stem cell therapy.

How should we do this together? In my view, through continuous combination of our complementary experience, education and expertise. That is what made it a success in the beginning and is key to the solutions of the future.

Pompe disease: Pathophysiology and Novel Approaches to Therapy

Nina Raben, M.D., Ph.D.
NIAMS, National Institutes of Health, Bethesda, Maryland

The clinical spectrum of Pompe disease, a deficiency of lysosomal acid alpha-glucosidase (GAA), ranges from fatal cardiomyopathy and skeletal muscle myopathy in infants to attenuated late-onset myopathy in adults. The only available treatment, designed to provide the missing enzyme, proved to be successful in reversing cardiac but not skeletal muscle abnormalities. The failure of the therapy to fully deliver on its promise has been due not only to the inefficient drug supply to muscle but also to the inadequate and entrenched view of the disease pathogenesis: enlargement of glycogen-filled lysosomes and lysosomal rupture leading to muscle destruction.

We have shown that the pathological cascade in muscle involves dysfunctional autophagy and inhibition of the autophagic flux. Another abnormality is the accelerated production of large lipofuscin deposits - a sign of mitochondrial dysfunction. Indeed, damaged mitochondria with reduced $\Delta\Psi_m$ and altered calcium buffering capacity, a decreased oxygen consumption and ATP production, and defective mitophagy were detected in Pompe muscle. The disease has the characteristics of autophagic myopathy, premature muscle ageing/lipofuscinosis.

Several new therapeutic approaches have been successfully tested *in vitro* and in GAA-KO mice: suppression of autophagy, modulation of calcium levels by Ca^{2+} channel blockers, and restoration of autophagic flux by the over-expression of TFEB and TFE3, the two transcriptional regulators of lysosomal-autophagosomal biogenesis. In addition, we have recently identified a dysregulation of mTORC1 signaling pathway, which is linked to the lysosomes. mTORC1, a master regulator of cellular growth and metabolism, is directly involved in the control of muscle mass. Reversal of this metabolic defect can halt skeletal muscle loss, a hallmark of Pompe disease.

Stem Cell Presentation

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Skeletal muscle is challenged to regenerate following trauma or exercise. This process is extremely efficient. Studies using laboratory mice have shown that adult muscle stem cells, termed satellite cells, are essential for this process. In human diseases affecting skeletal muscle, the balance between muscle regeneration and muscle wasting is disturbed. In Pompe disease, skeletal muscle fibers are progressively lost due to lysosomal glycogen accumulation. How satellite cells respond to Pompe disease is largely unknown. We have quantified the number of satellite cells in skeletal muscle biopsies from classic infantile, childhood, and adult onset Pompe patients. This showed similar satellite cell numbers compared to age-matched controls. The activation state of satellite cells to proliferate or differentiate was assessed, and this showed low levels of satellite cell activation similar to controls. Muscle regeneration, as measured by embryonic myosin heavy chain expression, was low to undetectable, despite severe muscle pathology. In contrast, biopsies from Duchenne Muscular Dystrophy patients showed high muscle regenerative activity. Understanding how satellite cells respond to Pompe disease may offer new options for therapeutic intervention via modulating the activity of endogenous satellite cells.

GAA Genotypes: What Do They Tell Us?

Arnold Reuser, Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

Genes are packages of information about how products, essential for the building and maintenance of the bodily structures, need to be made. The genes themselves are composed of chemical building blocks with the difficult name Desoxyribo-Nucleic Acids; abbreviated as DNA. There are only 4 different building blocks with the letters A, T, G and C. The order in which these letters are arranged within the gene (the genetic code) dictates what product will be made. Humans have an estimated 25,000 genes coding for minimally 25,000 products. The products being made are called proteins and consist of a chain of amino acids. There are 21 different amino acids, and the 25,000 different products encoded by the DNA differ by the order in which these 21 amino acids follow each other in the protein chain.

There are structural proteins that literally build structures like the wall of cells and structural proteins in the form of strings that hold tissue together. But there are also proteins that perform 'metabolic' functions such as the digestion of food. The latter kind of protein is called 'enzyme'.

Acid alpha-glucosidase (GAA) is one of the more than 25,000 proteins in the body. It is an enzyme and degrades glycogen, a polymer of glucose, into glucose (grape sugar). Patients with Pompe disease have an error in their gene (DNA) that codes for GAA. As a result, they make no GAA, or just a little GAA, or a GAA that does not perform its function very well. As a result the degradation of glycogen to glucose is totally or partially deficient, and patients with Pompe disease accumulate glycogen, which interferes with muscle function.

Since GAA deficiency is caused by a genetic error (an error in the DNA of the GAA gene), the nature of the error primarily dictates its biochemical and clinical effect.

I will discuss the power as well as the limitations of DNA analysis for predicting the clinical phenotype and progression of Pompe disease across the clinical spectrum.

Modifying Factos Presentation

Cesare Danesino, M.D.
University of Pavia, Italy

Glycogen storage disease type II (Pompe disease) is a rare genetically determined disorder.

The inheritance is autosomal recessive, thus many families are known in which more than one case is present. Of course, siblings share the same mutations, but still clinical presentation may be quite different. As environmental factors are unlikely to play a major role, other genetic factors must be present.

We studied some genes (as ACE and ACTN3) in whom genetic polymorphism able to modify the function of the gene are present, and found that they may act as modifier of some details of the clinical picture.

We have also started to study the same genes to study if the same polymorphisms may modulate the response to therapy.

We present also some ideas for future work based on our experience in different rare genetic disorders studied in our lab.

Micro-RNAs as potential biomarkers in Pompe disease

Giancarlo Parenti, M.D.
Federico II University, Naples

The availability of objective, reliable and reproducible tests is important to assess disease progression, to monitor efficacy of therapies, and to define criteria for starting enzyme replacement therapy in Pompe Disease (PD) patients. A broad range of clinical measures that require the expertise of skilled physicians are commonly used to evaluate patients, together with a few biochemical markers. The identification of additional biochemical indicators that are not influenced by inter- and intra-investigator variance would be desirable and may complement clinical tests.

We have evaluated micro-RNAs (miRNAs) as potential biomarkers for PD. MiRNAs are a growing class of small non-coding RNAs that interact with messenger RNAs, and regulate the expression of many genes and cellular processes. MiRNA are also expressed in blood. Their content in circulation may provide a read-out of altered pathways in response to disease conditions. In addition, since miRNAs regulate multiple cellular functions involved in disease development and progression, they may represent targets of therapeutic interventions.

We studied the expression of miRNAs in the PD murine model by using next generation sequencing (NGS), a powerful and innovative tool that allows large-scale analysis of genes and nucleotide sequences. MiRNAs profiles were studied in plasma and tissues from PD mice at two stages of disease progression, 3 and 9 months.

We identified one differentially expressed miRNA (DE-miRNA) in plasma at 9 months with statistical significance (FDR< 0.05). We also found 219 DE-miRNAs in muscle (gastrocnemius), and 35 DE-miRNAs in heart. In total, 104 miRNAs were differentially expressed at 3 months, 109 at 9 months, 42 were differentially expressed at both ages. Some of the DE-miRNAs are already known to modulate the expression of genes involved in pathways such as autophagy, muscle regeneration, inflammation that may be relevant for PD pathophysiology.

We also analyzed the levels of the circulating DE-miRNA in plasma samples from PD patients, obtained thanks to the collaborative effort of different Italian and Dutch centers. In 7 infantile-onset PD patients the mi-RNA levels were significantly higher than in age-matched controls. In samples from 27 late-onset patients, the levels were also higher, although not significantly.

These results suggest that circulating and tissue-specific miRNAs can represent novel biomarkers for PD. Future research, on larger cohorts of patients, should be aimed at defining the correlations of miRNA levels with phenotype, genotype, disease progression, age, gender, response to therapies. Additional studies should clarify the role of DE-miRNAs in PD pathophysiology.

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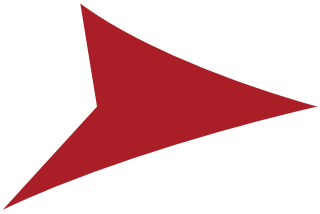

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