Enclosed please find the Agenda, Presenter Bios, and Abstracts on the Presentations that will be made.
Table of Contents

CONFERENCE AGENDA .......................................................... 1

PRESENTER BIOGRAPHIES .................................................. 3

ABSTRACTS ........................................................................ 11

ACKNOWLEDGEMENTS ...................................................... 18
# 2011 AMDA/IPA Pompe Patient and Scientific Conference Agenda

**Master of Ceremonies for the Conference: Dr. Arnold Reuser**

## Friday, October 7th, 2011

**Day at Sea World!**

Welcome Dinner at Sea World

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buses depart @ noon</td>
<td>Buses depart @ 5:30</td>
</tr>
</tbody>
</table>

## Saturday, October 8th, 2011

**Breakfast**

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome Address</td>
<td>8:00-8:10</td>
</tr>
<tr>
<td>History of Pompe</td>
<td>8:10-8:35</td>
</tr>
<tr>
<td>Introduction: What is Pompe?</td>
<td>8:35-8:50</td>
</tr>
</tbody>
</table>

**Enzyme Replacement Therapy & IPA/Erasmus Survey**

- 12 Years ERT experience with Infants
  - Dr. Priya Kishnani | 8:55-9:15 |
- 12 Years ERT experience with Late-Onset
  - Dr. Ans van der Ploeg | 9:15-9:35 |

Report from the IPA/Erasmus Pompe Survey

- Dr. Deniz Gungor | 9:35-9:55 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question and Answer</td>
<td>9:55-10:15</td>
</tr>
<tr>
<td>Break</td>
<td>10:15-10:30</td>
</tr>
</tbody>
</table>

**Industry Updates**

- Amicus Presentation
  - Nita Patel & Dr. Matthews Adera | 10:35-10:55 |
- BioMarin Presentation
  - Dr. William Lang | 10:55-11:15 |
- Genzyme Presentation
  - Dr. Alison McVie-Wylie & Dr. Tim Miller | 11:15-11:35 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question and Answer</td>
<td>11:35-12:00</td>
</tr>
<tr>
<td>Lunch</td>
<td>12:00-1:00</td>
</tr>
</tbody>
</table>

**Living with Pompe Panel**

- Respiratory Issues in Pompe Disease
  - Dr. John Bach | 1:05-1:25 |
- Swallowing, Dysphagia & Lingual Weakness in Pompe
  - Dr. Harrison Jones | 1:25-1:45 |
- Report on Erasmus Exercise Trial
  - Dr. Linda van der Berg | 1:45-2:05 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Perspective on Erasmus Exercise Trial</td>
<td>2:05-2:25</td>
</tr>
<tr>
<td>Question and Answer</td>
<td>2:25-2:55</td>
</tr>
<tr>
<td>Break</td>
<td>2:55-3:10</td>
</tr>
</tbody>
</table>

**Newborn Screening Panel**

- Results from Newborn Screening Study
  - Ria Broekgaarden | 3:15-3:35 |
- Results from Taiwan Newborn Screening Study
  - Dr. Y.T. Chen | 3:35-3:55 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challenges with Newborn Screening</td>
<td>3:55-4:15</td>
</tr>
<tr>
<td>Question and Answer</td>
<td>4:15-4:45</td>
</tr>
</tbody>
</table>

## Sunday, October 9th, 2011

**Breakfast**

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Future Research</td>
<td>7:30-8:30</td>
</tr>
</tbody>
</table>

**Autophagy and Pompe**

- Dr. Nina Raben | 8:35-8:55 |
- The Role of Antibodies
  - Dr. Priya Kishnani | 8:55-9:15 |
- Muscle Regeneration and Pompe
  - Dr. Ans van der Ploeg | 9:15-9:35 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question and Answer</td>
<td>9:35-9:55</td>
</tr>
<tr>
<td>Break</td>
<td>9:55-10:10</td>
</tr>
</tbody>
</table>

**Gene Therapy**

- Introduction to Gene Therapy | 10:15-10:25 |
- Dr. Andrea Amalfitano | 10:25-10:40 |
- Dr. Barry Byrne | 10:40-10:55 |
- Dr. Dwight Koeberl | 10:55-11:10 |
- Dr. Gerard Wagemaker | 11:10-11:25 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question and Answer</td>
<td>11:25-11:55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round Table Patient Discussion: Gaining Perspective</td>
<td>12:00-1:00</td>
</tr>
</tbody>
</table>

**Conference Close**
ANDREA AMALFITANO, D.O., PH.D.

Dr. Andrea Amalfitano is currently Professor of Pediatrics, Microbiology and Molecular Genetics, and holds the Osteopathic Heritage Foundation Endowed Chair in the College of Osteopathic Medicine at Michigan State University. He is a Diplomate of the American College of Medical Genetics, and a Fellow of the American Board of Medical Genetics.

Dr. Amalfitano received his Bachelor of Science in 1984, his Doctorate of Philosophy in 1989, as well his Medical Degree in 1990 at Michigan State University. He then completed Internal Medicine and Pediatrics Residency training, at Mt. Clemens General Hospital and the Mayo Clinic, before completing his medical specialty training in Human Medical Genetics at the University of Michigan.

Dr. Amalfitano was then recruited by Dr. Y.T. Chen and Duke University Medical Center into the Department of Pediatrics. While there, he not only cared for patients affected by any number of rare and sometimes devastating genetic diseases, but he also established a successful independent research effort focused on engineering viruses as genetic therapies for use in clinical medicine. Alongside Dr. Chen, Dr. Amalfitano co-led the first-in-man-study of a recombinant form of acid alpha-glucosidase (produced from cells engineered by Dr. Chen) as a potential therapy for Pompe patients. The pioneering study confirmed that such a therapy could prove beneficial, and paved the way to future studies that eventuated in the first FDA approved therapy for a muscular dystrophy. In fact, Dr. Amalfitano prescribes this medicine to a great number of Pompe patients he now sees during his clinical activities at MSU. Similarly, Gene Transfer vectors designed by Dr. Amalfitano are also being currently used in human clinical trials, targeting a variety of human diseases.

Dr. Amalfitano has several roles nationally and internationally, inclusive of being on numerous scientific advisory and review boards for several corporations, non-profit organizations and government agencies, inclusive of the NIH. He was appointed by Governor Granholm to the State of Michigan Newborn Screening Advisory, Quality Assurance and Improvement Panels, panels that oversee newborn screening for all infants currently born in the State of Michigan. In 2005, Dr. Amalfitano was very pleased to return to his alma mater, Michigan State University, where he continues to pursue not only his clinical care activities, and teach undergraduate, graduate and medical students, but he continues in his goal of translating cutting-edge biomedical research efforts into practical solutions for many of today's most difficult medical problems.

MATTHEWS ADERA, M.D.

Mathews Adera is the Medical Director of Clinical Research (Pompe, Fabry, and Gaucher) at Amicus Therapeutics from 2008 until present time. Mathews graduated from the University of Nairobi with his MBChB (MD equivalent) in 1992. He worked at Novartis Pharmaceutical Corporation from 2004 until 2008 where he was the associate Medical Director (Overactive Bladder, Women’s Health). While at Novartis, he also held the positions of Clinical Research Scientist (bone) and Study Manager (renal transplant). Mathews worked at GSK (Canada) from 2003-2004 where he was a Study Manager (Respiratory). Mathew worked at Pharmacia Canada as the Study Manager (Oncology, Endocrinology) from 2001-2001. Earlier in Mathew’s career, he worked at the D’Arcy Lane Institute, as a lecturer (Medicine and Pathology) from 1996-2001; at the University of Western Ontario where he worked as a Researcher (Physiology & Immunology) from 1994-1996; and at the Kenyatta National Referral Hospital- (physician) from 1993-1994. Mathews also worked at the Medecins San Frontiers, in France (physician) from 1992-1993; with the African Medical Research Foundation (Flying Doctors’ Service) from 1991-1992; and Medical Training College (Lecturer) in 1991.
**JOHN BACH, M.D.**

Dr. John R. Bach received his medical degree from the College of Medicine and Dentistry of New Jersey in 1976. He completed residency training in PM&R at New York University in 1980. Since returning from a two year fellowship in the rehabilitation of neuromuscular diseases in Pottiers, France in 1983, he has been on the faculty of the New Jersey Medical School-UMDNJ where he is an Assistant Professor of PM&R, Professor of Neurosciences, Vice Chairman of the Department of PM&R, Director of Research and Associate Medical Director of the Department of PM&R at University Hospital, Newark, N.J., Co-director of the medical school’s Jerry Lewis MDA Clinic, and medical director of the Center for Ventilator Management Alternatives and Pulmonary Rehabilitation. He has published over 350 articles and book chapters, 7 books, and has lectured on respiratory care at many scientific meetings both nationally and in over 40 countries.

**RIA BROEKGAAARDEN**

Ria Broekgaarden has been involved in Pompe disease for more than twenty years nationally and internationally. Based in the Netherlands at the VSN (the Dutch Neuromuscular disease organization) she was, and is, active in the IPA (International Pompe Association) first as a board member and at this moment as advisory board member. Her talk will be about Newborn Bloodspot Screening for Pompe disease.

**BARRY BYRNE, M.D., PH.D.**

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.

**YUAN-TSONG (Y-T) CHEN, M.D., PH.D.**

Professor Chen received his MD degree from National Taiwan University (Taipei) and PhD from Columbia University (USA). He is currently a Distinguished Research Fellow of the Institute of Biomedical Sciences, Academia Sinica, Taiwan, and Professor of Pediatrics at Duke University Medical Center (USA).

Professor Chen is a physician/scientist, recognized for his work on human genetic disorders. His translational research leads to the development of new standard therapies for two devastating inherited metabolic diseases: a simple and effective cornstarch therapy for severe hypoglycemia in glycogen storage diseases and an enzyme replacement therapy, the first ever treatment, for a debilitating, progressive and often fatal myopathy called Pompe disease. Professor Chen has also identified the genetic basis of and developed DNA-based diagnosis for several major heritable diseases, and more recently, his team in Taiwan has uncovered genes/SNPs associated with drug-induced Stevens-Johnson syndrome and warfarin sensitivity. His latest pharmacogenomic studies of adverse drug reactions paved the way for personalized medicine by preventing drug toxicity with a gene test. Professor Chen is an elected member of Academia Sinica and of the Academy Sciences for the Developing World.
DENIZ GUNGOR, M.D., MSc.

Deniz Güngör is a Ph.D. student at the Center for Lysosomal and Metabolic diseases at Erasmus MC Rotterdam, the Netherlands. She received her medical degree in 2007 at Erasmus University Rotterdam, after which she worked as a resident at the Department of Neurology at Sint Franciscus Gasthuis and Erasmus MC in Rotterdam. In 2011 she obtained her Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Science in Rotterdam. During her medical training she performed in 2004 a research project on Vitamin D deficiency in infants in a rural hospital in Samarkand, Uzbekistan (Supervisors: Dr. R. Rodrigues Pereira and Dr Alisher Rasulov).

In 2008 she joined the Pompe research team of Professor van der Ploeg and Dr. Arnold Reuser. The title of her research project is "Investigation into the clinical condition of Pompe patients - IPA/Erasmus MC Pompe Survey: Effects of enzyme replacement therapy compared with natural course." The goal of this project is to better understand the variability and progression of Pompe disease by gathering information on the clinical course and severity of the disease, and the impact on the daily life of the patients. Furthermore, the long-term effects of available treatment options will be evaluated.

HARRISON JONES, PH.D.

Harrison N. Jones, PhD, BRS-S, CCC-SLP, Assistant Professor, Department of Surgery, Division of Speech Pathology & Audiology, Duke University. Dr. Jones received his PhD from the University of Florida in Rehabilitation Science in 2007. He has been practicing as a speech pathologist for over ten years and continues to spend half his time in the clinic. Dr. Jones has published many peer-reviewed journal articles. Additionally, he is co-author of the book Dysphagia in Movement Disorders, co-editor of Dysphagia in Rare Conditions, and the author of many book chapters. His current research program is focused on speech, swallowing, and respiratory disorders in genetic diseases across the lifespan and their rehabilitation via exercise-based, behavioral approaches. Currently funded research projects are focused on adults and children with Down syndrome and Pompe disease.

Dwight Koebel, M.D.

Dr. Koebel 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 has also served as Medical Director for the Pediatrics Biochemical Genetics Laboratory and sees patients in the Metabolic Clinic. Recently his laboratory has developed a small molecule therapy to enhance the response to ERT or gene therapy in Pompe disease, which is the topic for his presentation today.
PRIYA KISHNANI, M.D.

Dr. Kishnani moved to the United States in 1991 after completing a residency in Pediatrics in Mumbai, India. She completed a fellowship in clinical and biochemical genetics at Duke University Medical Center in 1995 and shortly thereafter joined the faculty at Duke University. Dr. Kishnani is certified by 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. The care, treatment and natural history of individuals with lysosomal storage disorders (LSDs), glycogen storage diseases (GSDs), Down syndrome (DS) and other inborn errors of metabolism remain her passions. Her areas of publication include treatment strategies, examination of long-term complications and the results of a number of clinical trials for multiple disorders. 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. Her team at Duke University Medical Center is well recognized internationally for the contributions made to the field of Pompe disease.

Dr. Kishnani has been instrumental in uncovering several long-term complications in Pompe disease, including osteopenia, speech and swallowing dysfunction, pulmonary issues, lingual weakness, cardiac arrhythmias, vascular involvement and sleep apnea. She has played a pivotal role in identifying prognostic factors such as role of CRIM status and antibody titers in clinical response to ERT. She has expertise in design/determining end points for clinical trials for diseases such as Pompe disease, Down syndrome and other LSDs and has also been active in investigating long-term complications and the natural history of several other disorders in addition to Pompe disease. She is currently investigating treatment strategies for the immune responses to Pompe disease and ways to enhance enzyme delivery to skeletal muscle.

She is Chair of the North American Pompe Registry Board and is a member of the International Pompe Registry Board of Advisors. She is also a member of the North America Gaucher Registry Board. Dr. Kishnani is Chair of the Scientific Advisory Board for AGSD, US.

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’s 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, and the, “Christian Pueschel Memorial Research Award for outstanding clinical research that improves lives through greater understanding of Down Syndrome” by the National Down Syndrome Congress..

Dr. Kishnani is the Chief of Medical Genetics and the medical director of the YT and Alice Chen Pediatrics Genetics and Genomics Center, which has a focus on developing new therapies for rare genetic disorders.

Dr. Kishnani is the proud mother of two wonderful and beautiful children, Kunal, 18 and Sujata, 14. In her spare time, Dr. Kishnani enjoys dining out, vocal music, entertaining in her home and volunteering at her children’s school. She knows that she would be unable to succeed in her work without the love and support of her husband, Sunil.

WILLIAM LANG, M.D., F.A.C.P.

Dr. Lang has 13 years of experience in drug development in the fields of virology, oncology, nephrology and rare diseases. He is board certified in Internal Medicine and became a pharmaceutical physician after 15 years of the clinical practice of internal medicine, and after serving as principal investigator on more than 100 clinical trials during that time. He is currently Senior Medical Director at BioMarin Pharmaceutical.
ALISON McVIE-WYLIE, PH.D.

Alison McVie-Wylie is the Scientific Director of the Pharmacology and Toxicology group at Genzyme Corporation. Alison manages a group of scientists who design, execute, interpret and report studies to support preclinical drug development of novel biologic therapeutics. Alison was the lead Scientist responsible for the preclinical development and licensure of Myozyme. Prior to Genzyme, Alison worked in the laboratory of Dr. Y.T. Chen at Duke University on the early development of recombinant human acid alpha-glucosidase (rhGAA) as a treatment for Pompe Disease. At Duke University, Alison also became board certified in Clinical Molecular Genetics. Alison obtained her Ph.D. in Molecular Genetics from the University of Glasgow, Scotland, and a B.Sc. in Biochemistry and Immunology from the University of Strathclyde, Glasgow.

TIMOTHY MILLER, M.D.

Dr. Timothy Miller is a board certified neurologist and fellowship trained neuromuscular expert who currently serves as medical director within the Medical Affairs arm of the Personalized Genetic Health Division of Genzyme, a Sanofi company. In this role, Dr. Miller focuses on helping health care professionals and payors make evidence-based decisions that optimize health outcomes for patients and supports Genzyme’s mission of providing expertise on current and emerging therapies.

In addition to his work with Genzyme, Dr. Miller also maintains academic appointments in the Departments of Neurology and Pediatrics at the University of Arizona and a clinical practice, directing the Muscular Dystrophy Association’s Comprehensive Neuromuscular Clinic at the Children’s Clinics for Rehabilitative Services in Tucson, Arizona. Dr. Miller pursued neurological training and fellowship activities at Baylor College of Medicine in Houston, Texas, the University of Arizona in Tucson, Arizona, and at Washington University in St. Louis, Missouri. He has been involved in clinical and basic science research in various neuromuscular diseases, including the muscular dystrophies and motor neuron disorders and continues these efforts with collaborators at Genzyme and in the academic world. Dr. Miller has qualifications and memberships in multiple professional societies, including the American Academy of Neurology and the American Association of Neuromuscular & Electrodiagnostic Medicine.

KEVIN O’DONNELL, PH.D.

Dr Kevin O’Donnell is based in Edinburgh, Scotland. Although a professional scientist, his interest in Pompe disease is personal; he and his wife Elaine lost their first child, Calum, to the disease in 1993.

For the next 10 years he was active in the growing Pompe patient community and witnessed the development of enzyme replacement therapy from a lab-based concept to a full-scale treatment. Although ‘retired from active Pompe service’, he was prompted by the inaccuracies in the film Extraordinary Measures to put on record the real story of the development of a treatment for Pompe disease via his blog, pompestory.blogspot.com.

Kevin and Elaine also have two children not affected by Pompe disease.

NITA PATEL, R.N.

Nita is the Associate Director of Patient Advocacy at Amicus Therapeutics. Nita started her nursing career as a midwife in London England, and since then she developed an interest in genetics and started to work at the Institute for Genetic Medicine at St. Peter’s University Hospital where she helped start the Lysosomal disease (LSD) center. Nita managed the LSD center for over 20 years. Due to a new interest in clinical research and because of her vast clinical experience with LSD patients, Nita chose to move her career towards patient advocacy in Pharma.

Nita has recently rejoined the team at Amicus Therapeutics as an Associate Director, Patient Advocacy, prior to that she was working as a Medical Science Liaison and Patient Advocacy at Pfizer Inc.
**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 years have been focused on muscle diseases, both immunological and genetic, and for over the past 15 years, his research has centered on Pompe disease, particularly the need to develop effective therapy for the skeletal muscle disease. He remains at NIH as a Scientist Emeritus, still attached to his research and clinical groups.

**NINA RABEN, M.D., PH.D.**

Staff Scientist, Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health, Bethesda, MD.

Dr. Raben was born in Moscow, Russia (the former Soviet Union). She received her medical degree from the Moscow Medical Institute, and Ph.D. degree in Biochemistry from the National Academy of Medical Science, Moscow. Dr. Raben joined NIAMS in 1990, and since then has been working on inflammatory and metabolic myopathies. The major focus of her research in recent years is Pompe disease. Her studies include mutational analysis of the gene, development of several knockout and transgenic mouse models of the disease, extensive pre-clinical studies with recombinant human enzyme, and investigation of the role of autophagy in the pathogenesis of Pompe disease.

**ARNOLD REUSER, PH.D.**

Life does not always proceed along a carefully planned path. I was lucky to be born without having an inherited disease that would have affected my life un-willfully. Thanks to my genetic constitution, my living environment and the dedicated care of my parents, I had an uncomplicated youth and the ability to go to university. But, what direction to chose? It became chemistry and physics for not very obvious reasons. After two years of hard labor, the application of these two disciplines to biological systems became most appealing to me, and that is how I graduated from the University of Amsterdam with a Master of Science degree in biochemistry, which discipline studies the chemistry and physiology of life. After that, the unexpected happened. Within no time I got offered two jobs, one at the University of Amsterdam to study Pompe disease (Acid Maltase Deficiency) and one at the University of Rotterdam to do the same. At that time, it was 1973, I had never before heard about Pompe disease, but concluded that it had to be a very important topic. I took the job at the Erasmus MC University Medical Center in Rotterdam, became research scientist, wrote my PhD thesis about the cause of clinical diversity in Pompe disease and, fascinated by the project and its challenges, continued my research in the field of Pompe disease till to date, while fulfilling in between demanding but rewarding duties as professor in Cell Biology and Microscopical Anatomie.
MARYZE SCHONEVELD VAN DER LINDE

Maryze Schoneveld van der Linde, MA was born in 1970 and lives in the Netherlands. She studied Cultural Anthropology and graduated at the University of Leiden, The Netherlands, in 1995. Since 1996 she has been working with migrant and refugee women from Turkey and the Middle East Region in empowerment related issues and activities. She was born with a hereditary neuromuscular disorder called Pompe’s disease or Glycogen Storage Disease type 2. The diagnosis was made at the age of 8 years. She has been an active board member of the Dutch Association for Respiratory Support (VSCA, 1997 - 2006) and an active board member of the International Pompe Association (IPA, 1999 - 2006). During this period she played a key role in getting reimbursement and market approval for enzyme replacement therapy to treat Pompe disease. Currently she is an advisor of the IPA (www.worldpompe.org).

In 2007 she started a consultancy in health and care called Patient Centered Solutions (www.pacesworld.com) to take care of her own income. With her consultancy she provides clients with experienced based expertise, knowledge and practical insights from a patient’s perspective. She focuses especially on rare diseases, orphan drugs development and patient involvement, reimbursement, raising awareness on diseases etc.

From February 2009 till 2011 she worked as a project manager for the European Neuromuscular Centre (www.enmc.org) for the EU project called TREAT-NMD (www.treat-nmd.eu). This EU project started to advance diagnosis, care and treatment for people with neuromuscular diseases around the world. In this project Maryze was responsible for the active involvement of patient organisations in Europe in issues related to care, (orphan) drug development, clinical trial design, patient registries, creating networks, ethics etc.

Since June 2010 Maryze has initiated and led the international working Group ‘Flying with Ventilation’ to address the increasing problems people with ventilation experience when wanting to travel by plane and to find a permanent solution for it at EU level. In response the EU Commission will start a consultation in October 2011 on the Regulation (EC) No. 1107/2006 of the Parliament and of the Council of 5 July 2006.

Since September 2011 she works for the Dutch Genetic Alliance (www.vsop.nl) where she is employed to involve patient organisations and patients in the EU project ‘Global Research in Paediatrics (GRIP)’ to provide children with safe and effective medicines.

Awards:

In May 2011, Maryze received the Angel Award for Rare Diseases 2011. This Award is granted in the Netherlands to someone for extraordinarily work, commitment and dedication that had a significant impact for rare diseases and Pompe Disease in particular.

In September 2010 Maryze received a Leadership Award/Certificate from the UILDM (Italian Neuromuscular Disease Association) for commitment in connecting and empowering people with a neuromuscular disease.

WILMA TREUR

Wilma Treur is a Pompe patient. She lives in the Netherlands and has a job where she works at local municipality in the Haarlemmermeer three days a week. She has a daughter that is 14 years old. Wilma was diagnosed in 2004 and has been on treatment with Myozyme since 2007.

Wilma also works as a volunteer for the VSN (the Dutch neuro muscular disease organization) and she is a board member of the IPA (International Pompe Association).
**LINDA VAN DER BERG, M.D., M.Sc.**

Dr. van den Berg is a Ph.D.-student at the Center for Lysosomal and Metabolic Diseases. She studied Movement Sciences and received her M.Sc. in 2002 from the University of Maastricht. She received her M.D. in 2007 from the Erasmus University. Since 2007 she has been working on her PhD at the Department of Paediatrics of the Center for Lysosomal and Metabolic Diseases. The title of her thesis will be “The effects of enzyme replacement therapy on the musculoskeletal system in Pompe disease.”

**PROF. ANS VAN DER PLOEG, M.D., PH.D.**

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.

She 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.

**GERARD WAGEMAKER, PH.D.**

Gerard Wagemaker, PhD, trained in medicine, radiation and transplantation biology, is currently head of the section of Stem Cell Gene Therapy and Professor of Hematology, Chair of Gene Therapy, at the Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands. He is author of more than 180 publications with a long-standing record as coordinator of inherited diseases gene therapy projects subsidized by the European Commission, which significantly contributed to the current position of European science in the development of gene therapy for inherited disorders. He was involved in the development of stem cell transplantation for SCID and osteopetrosis (Lancet, 1986); his group was among the first to identify the selective advantage of the progeny of normal hematopoietic stem cells in thalassemia (Transplantation, 1986) and in brain cells in Krabbe's disease (Science, 1988), and among the first to demonstrate the versatile use of the green fluorescent protein to study both the efficiency of gene transfer and stem cell biology (Blood, 1997). Currently, his research group conducts research directed at development of lentiviral vector gene therapy for immune deficiencies (SCID-X1, RAG1 and 2) and lysosomal storage disorders with special emphasis on Pompe disease (Blood, 2010), as well as more basic research in the fields of ex vivo stem cell amplification and stem cell genomics. The gene therapy research is supported by two large-scale integrated projects in the research framework program of the European Commission, in which all leading European gene therapy centers for inherited disorders collaborate, and by a program subsidy of The Netherlands Organisation for Health Research and Development ZonMw. He is president of the Netherlands' Society for Gene and Cell Therapy and member of the European Union Committee of Experts on Rare Diseases.
The History of Pompe Disease
Kevin O’Donnell, Ph.D.

This presentation summarizes the history of the development of enzyme therapy for Pompe disease. Starting from its discovery by J C Pompe in 1932, it charts the evolution of our understanding of the disease, showing how this was dependent upon scientific progress in other fields. Improved understanding of the nature of Pompe disease led to the search for treatments, which has so far led us to enzyme replacement therapy (ERT). The scientific and industrial development of ERT is shown to be intertwined with another story, that of the growth of an international Pompe community. These threads combine to form a compelling narrative of patients, scientists and industry working towards a common goal - and reaching it. An understanding of our past - what went wrong and what went right - will help ensure better understanding of the present and better planning for the future.

12 years ERT Experience with Infantile Pompe Disease
Priya Kishnani, M.D.
Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center

Enzyme replacement therapy (ERT) with alglucosidase alfa for infantile Pompe disease (IPD) has improved survival. Improved survival has also led to a number of unanswered questions regarding the clinical course of treated disease. We describe an emerging phenotype in long-term IPD survivors. We will discuss clinical outcomes of babies with infantile Pompe disease that have received ERT for at least five years. Inclusion criteria for this study included ventilator-free status and age ≤6 months at ERT initiation, and survival ≥5 years age. Clinical outcome measures included invasive ventilator-free survival and parameters for cardiac; pulmonary; musculoskeletal; gross motor and ambulatory status; growth; speech, hearing, and swallowing; and gastrointestinal and nutritional status. Laboratory-based measures included anti-alglucosidase alfa antibody titers, and urine and serum biomarker trends (urine hex 4, CPK, AST, ALT). All long term survivors had marked improvements in cardiac parameters and were capable of independent ambulation. Commonly present were gross motor weakness, motor speech deficits, sensorineural and/or conductive hearing loss, osteopenia, gastroesophageal reflux disease and dysphagia with aspiration risk. Overall, biomarker trends remained stable. All long-term survivors had low or undetectable antibody titers against alglucosidase alfa. Long-term survivors with IPD exhibited sustained improvements in cardiac parameters and gross motor function. Residual muscle weakness, hearing loss, risk for cardiac arrhythmias, hypernasal speech, dysphagia with risk for aspiration and osteopenia were commonly observed findings. Further, although there are some phenotypic similarities shared with late-onset patients, there also exist key distinguishing features. This cohort of long-term survivors of infantile Pompe disease provides a contextual basis for the emerging phenotype and relevant issues in clinical management. Continued systematic follow-up is needed to better characterize this emerging phenotype and to allow for improved patient management. Factors that impact outcome, the dose of alglucosidase alfa and implications on patient care will be discussed.
Twelve years enzyme replacement therapy (ERT) experience in Late-Onset Pompe disease

Prof. Ans van der Ploeg, M.D., Ph.D.
Department of Pediatrics, Division of Metabolic Diseases and Genetics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Pompe disease is a progressive inheritable disorder caused by the deficiency of lysosomal acid alpha-glucosidase required for the degradation of glycogen. Deficiency of alpha-glucosidase leads to glycogen storage in various tissues, but predominantly muscles. The incidence of the disease worldwide is 1 in 40.000.

The disease may present at any age and reflects in fact a spectrum of disease presentations.—Patients with the most severe classic infantile form harbour two severe mutations in their alpha-glucosidase (GAA) gene and express virtually no residual alpha-glucosidase activity. They present shortly after birth with feeding difficulties, muscle weakness, and a hypertrophic cardiomyopathy. Without therapy these patients usually die within the first year of life due to cardiorespiratory failure. The majority of patients with Pompe disease present at later age. In these child and adult patients generally one of the two mutations in the GAA gene is less severe. As a result the disease presents as a more slowly progressive muscle disorder affecting mainly the proximal limb girdle muscles and respiratory muscles. Cardiac hypertrophy is rarely seen especially in adults with Pompe disease. Fifty percent of children and about 80 percent of adults express the same GAA mutation leading to 10-20% residual alpha-glucosidase activity.

Erasmus MC has a more than 25 year long history with respect to research on Pompe disease and development of enzyme therapy. Important milestones were cloning of the GAA gene, generation of a mouse model for Pompe disease, exploration of production methods for recombinant human alpha-glucosidase by use of the human coding sequence of the alpha-glucosidase gene and successful feasibility studies in cells form patients and the generated mouse model for Pompe disease.

This has led in 1999 to the first enzyme therapy study in humans. For this purpose recombinant human alpha-glucosidase produced in milk from transgenic rabbits was used. In this pilot trial four infants, two children and one adult were enrolled from the Netherlands, Belgium and the USA. Currently after 12 years 6 of these patients, are alive. Subsequent international trials in both infants and adults have gradually increased the understanding of the potential of enzyme therapy. A lot has been learned but the learning process has not been completed yet. Many questions are still unanswered.

Currently, the center for Lysosomal and Metabolic Diseases, the sole referral center for Pompe disease in The Netherlands, treats over 100 patients, infants, children and adults, with enzyme therapy. The majority of these patients are patients with late onset Pompe disease. All patients are followed by standardized IRB approved follow-up programs. In part of these patients these follow-up programs were already initiated in the years before start of enzyme replacement therapy enabling us to compare pre- and post-treatment data.

During the presentation an update on the results obtained in patients with late onset Pompe disease receiving enzyme therapy will be given.

Results of the IPA/Erasmus MC Pompe Survey

Deniz Güngör, M.D., MSc
Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, the Netherlands

In 2002, Erasmus MC and the International Pompe Association (IPA), the worldwide federation of patient groups, started an international study (the IPA/Erasmus MC Pompe Survey) in children and adults with Pompe disease by means of self-report questionnaires in order to improve the understanding of the natural course of Pompe disease, the impact of the disease on daily life of patients and the effects of innovative therapies. Since the start of the study, patients completed questionnaires on an annual basis. At this moment more than 300 Pompe patients have participated in the survey through the IPA-affiliated patient organizations in the United States, the United Kingdom, the Netherlands, Germany, France, Canada and Australia. Thanks to the continued and ongoing participation of patients and patient organizations the study has led to improved insights and various publications in peer reviewed international journals.

During today’s presentation, the latest results of the IPA/Erasmus MC Pompe Survey will be discussed. Recent studies have focused on the impact of Pompe disease on the life expectancy of (adult) patients. So far, data on life expectancy were available for infants but not for adults. Information on life expectancy in adult Pompe disease and effects of enzyme therapy on life expectancy have become increasingly important since reimbursement agencies are requesting this type of information for decision making.

Additionally, we assessed the effect of ERT on fatigue. Previous results from the Survey have shown that fatigue is a prominent disabling symptom in patients with Pompe disease.

BMN 701: A Promising Therapy for Pompe Disease

William Lang, M.D.
BioMarin

BMN 701 is a fusion protein utilizing the superior in vitro uptake of IGF-2 at the mannose 6 phosphate binding site to significantly increase delivery of rhGAA to cellular lysosomes. In addition to superior kinetics, data in the mouse Pompe model data show that BMN 701 clears glycogen as well or better at the same or lower doses than rhGAA. This data as well as the design of the currently enrolling Phase 1/2 clinical trial will be presented.
Respiratory Issues in Pompe Disease
John Bach, M.D.
Department of Physical Medicine and Rehabilitation, University of Medicine and Dentistry of New Jersey (UMDNJ), New Jersey Medical School.

The purpose of this lecture is to describe the use of noninvasive inspiratory and expiratory muscle aids to prevent ventilatory insufficiency and failure, and to permit the extubation and tracheostomy tube decanaluation of “unweanable” patients. Noninvasive airway pressure aids can provide up to continuous ventilator support for patients with little or no vital capacity and can provide for effective cough flows for patients with severely dysfunctional expiratory muscles. An April 2010 consensus of clinicians from 22 centers in 18 countries reported 1623 NIV users, of which 760 developed continuous ventilator dependence to prolong survival by over 3000 patient-years without tracheostomies. Four of the centers routinely extubated unweanable patients so that none of their over 250 such patients has undergone tracheostomy. Since bulbar-innervated (throat) muscle function is general preserved in patients with acid maltase deficiency, and total loss of throat muscle function is the only valid indication for tracheotomy, patients with AMD rarely if ever require tracheostomy tubes for ventilatory support.

Bulbar Muscle Involvement in Pompe Disease: Speech and Swallowing Disorders in the Setting of Lingual Weakness
Harrison N. Jones, M.D. & Priya Kishnani, M.D.
Duke University, Department of Surgery, Division of Speech Pathology & Audiology, Durham, NC

Pompe disease is traditionally conceptualized as having a primary distribution involving the skeletal, cardiac, and smooth muscles. However, accumulating data also suggest that prominent bulbar muscle weakness is present in both the infantile- and late-onset phenotypes. The bulbar muscles comprise the cranial nerve innervated muscles of the face and neck used primarily for speech and swallowing via brainstem sensorimotor nuclei and higher cortical controls. Speech and swallowing disorders have become increasingly recognized in Pompe disease, especially in the infantile-form. Although the exact mechanism of these deficits is unknown, they are likely due, at least in part, to glycogen deposits in the bulbar muscles responsible for speech and swallowing. This suggests that speech and swallowing disorders in Pompe are neurologically-based disorders due to lower motor neuron involvement resulting in weakness and hypotonia of the speech and swallowing mechanisms. Recent data have also reported the presence of lingual weakness in 100% of 19 adults with late-onset disease, including two with asymptomatic disease. Lingual weakness may thus emerge as an early sign of Pompe disease. Additionally, the functional consequences of bulbar muscle involvement, including speech and swallowing disorders, may be continue to emerge with the extended lifespan afforded by enzyme replacement treatment (ERT).

Effects and Safety of Exercise Training in Patients with Late-onset Pompe Disease Receiving Enzyme Replacement Therapy for a Longer Period
L.E.M. van den Berg, M.D., M.Sc.
Department of Pediatrics, Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Pompe disease (glycogen storage disease type II, acid maltase deficiency) (OMIM 232300) is an inherited lysosomal storage disorder caused by the deficiency of acid α-glucosidase. Deficiency of this lysosomal enzyme leads to glycogen accumulation in predominantly skeletal muscles. Slowly progressive proximal muscle weakness is the main feature in children and adults with Pompe disease.

Enzyme replacement therapy in children and adults has shown to elicit positive effects on muscle function, but not all patients respond equally well. Exercise training programs have shown to elicit positive effects on oxidative capacity and muscle function in other myopathies than Pompe disease. Only a few studies on exercise training have been published for adult Pompe disease, all with small sample sizes. At present there are no guidelines for trainings programs in Pompe disease. This was the reason for performing a randomized control trial in 25 patients on the additional effects and safety in adult patients with Pompe disease receiving enzyme replacement therapy. Patients were randomly subdivided into two groups. All subjects followed a 12 week lasting program of supervised aerobic, progressive resistance and core stability exercise training. Group 1 started to follow the exercise training program for three months. Group 2 served as control group for the first three months and started to follow the training program for the next three months. Before and after the training period the effects on endurance, muscle strength, muscle function body composition and well-being were assessed. The preliminary results of this study will be presented.

Patient Perspective on Erasmus’s Pompe Patient’s Sports Program
Wilma Treur, VSN

Wilma Treur’s presentation is about her experiences with a specifically designed Pompe Patients Sports program. This program was developed in Rotterdam, the Netherlands at Erasmus University Medical Center.

During the months of May, June, and July, Wilma trained three times a week for almost two hours. During this presentation Wilma will inform you about the results and effects—the advantages and disadvantages of this sports program!
Newborn Bloodspot Screening for Pompe disease

Ria Broekgaarden, VSN

Treatment is available for Pompe disease. Early diagnosis and early intervention is to the benefit of patients and their families and increases the chance to achieve an optimal therapeutic effect. The ultimate way to speed up diagnosis is universal newborn screening. Pompe disease has a broad clinical spectrum and newborn screening will probably not just identify patients who will develop symptoms within a few months after birth, but also persons who will develop symptoms at later age. There are advantages and disadvantages of newborn screening. Results of a survey done amongst people with Pompe disease and the general public will be addressed.

Newborn screening for Pompe disease: Taiwan’s experience

Yuan-Tsong (Y-T) Chen¹, Yin-Hsiu Chien¹, Wuh-Liang Hwu²

¹Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan and Department of Pediatrics, Duke University, Durham, NC, USA, ²Department of Medical Genetics and Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

Pompe disease is an autosomal recessive lysosomal storage disorder caused by deficient acid α-glucosidase (GAA) activity, which results in glycogen accumulation and progressive, debilitating, and often life-threatening symptoms, involving musculoskeletal, respiratory, and cardiac systems. The recent development of enzyme replacement therapy (ERT) has dramatically improved the outcome of the disease; however, limitations of the therapy such as high dose and variable skeletal response remain a challenge. Stage of the disease at the time of treatment, CRIM status of the patients and antibody are some important factors contributing to the variable skeletal response.

A large-scale newborn screening pilot program was conducted in Taiwan from October 2005 to March 2008. The screening involved measuring GAA activity in dried blood spots (DBS) in approximately 45% of newborns in Taiwan. The unscreened population was monitored as a control. After this study, all newborns in Taiwan received GAA screening on voluntary basis.

Up to December 2009, 344,056 newborns were screened and 19 were confirmed to have Pompe disease. The incidence of all types of Pompe disease detected by the newborn screening program was approximately 1 in 18,108. Six newborns showed hypertrophic cardiomyopathy during the neonatal period and were classified as having infantile-onset Pompe disease; they were treated within a week after the diagnosis. They all demonstrated normalization of cardiac size and muscle pathology with normal physical growth and age-appropriate gains in motor development.

Thirteen newborns with deficient skin fibroblast GAA activity and two GAA gene mutations but no cardiomyopathies were assumed to have later-onset Pompe disease, and their motor development and serum creatine kinase (CK) were followed every 3-6 months. During a follow-up period of up to 4 years, 4 of them were treated because of hypotonia, muscle weakness, delayed developmental milestones/motor skills, or elevated CK starting at the ages of 1.5, 14, 34 and 36 months, respectively. Muscle biopsies obtained from the treated patients revealed increased storage of glycogen and lipids.

This large-scale study shows that newborn screening for Pompe disease is feasible. This study also demonstrates that early treatment can benefit infants with Pompe disease and highlight the importance of early diagnosis, which can be achieved by newborn screening.

Challenges with Diagnosis and Newborn Screening

Arnold Reuser, Ph.D.
Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, the Netherlands

The clinical presentation of Pompe disease / Acid Maltase Deficiency is well described despite the disease being very rare. Nevertheless, it remains a challenge to recognize affected individual timely and to confirm the diagnosis quickly with presently available technologies. Diagnostic delays are caused by unawareness due to rarity of the disease, and by application of wrong diagnostic methodologies. Misdiagnoses are caused by the use of sub-optimal diagnostic materials and by misinterpretation of the diagnostic results.

The general awareness is typically increased through activities of patient associations like the AMDA and her sister associations throughout the world, unified in the IPA, the International Pompe Patient Association. Awareness is further fortified by the investment of industrial partners like Genzyme, BioMarin, and Amicus developing new therapies and commercial activities in the field of Pompe disease. The keen eye of the doctor will always be required to initiate diagnostic testing, and the experience of the laboratory to decide for the best diagnostic approach.

Newborn screening reduces the role of physicians in the diagnostic process as the screening activity identifies the disease before the onset of clinical symptoms. Newborn screening changes the role of physicians from being professionals that are able to recognize clinical symptoms and to order proper enzymatic or genetic diagnostic testing to professionals that are able to translate enzymatic, biochemical, and genetic findings into a prospective disease phenotype, and subsequently initiate timely intervention without laying too much of a burden on the shoulders of the prospected patient. Various methodologies and current strategies to diagnose Pompe disease will be discussed.
**Autophagy in Pompe Disease**

Nina Raben, M.D., Ph.D.
Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

Autophagy has attracted considerable attention because of its role in a wide variety of diseases. Autophagy is a “self-eating” process that brings cytoplasmic cargo enclosed in double-membrane autophagosomes to lysosomes for digestion and recycling. We have shown in our Pompe mouse model (GAA KO) that autophagic buildup is largely responsible for muscle damage and for the poor muscle response to enzyme replacement therapy (ERT). Furthermore, the genetic suppression of autophagy in Pompe mice resulted in the reduction of glycogen load and near-complete glycogen clearance upon ERT. With many pharmaceutical companies actively working to develop autophagy inhibitors, suitable models to test and screen for such compounds are needed. For this purpose we have generated transgenic GAA KO mice expressing the autophagosomal marker LC3 linked to GFP. These GFP-LC3:GAA KO mice exhibit autophagic buildup in myofibers, and thus provide an adequate model of the disease and a useful tool for monitoring changes in autophagy.

Autophagic abnormalities are present in many muscle cells in late-onset patients (both juvenile and adults), thus making the observations in a mouse model relevant to the human study. Moreover, in many fibers from human biopsies autophagic accumulation is the overwhelming (and in some fibers the only) pathology, because the lysosomes that lie outside the autophagic region appear essentially normal. Unexpectedly, the autophagic component which is so prominent in late-onset cases was insignificant in a group of infants whose biopsies became available for analysis. Although the components of the autophagic system are made in excess and occasional enlarged autophagosomes are clearly seen in muscle fibers, the autophagic buildup is absent. Instead, the major characteristic of these fibers is the presence of hugely expanded lysosomes without clear borders, a finding consistent with the hypothesis of lysosomal rupture as a cause of muscle destruction. However, analysis of follow-up biopsies from infants on ERT shows that autophagic buildup resembling that found in muscle from adults emerges on therapy; this buildup persists after years of treatment and may well be the reason for unsatisfactory clinical response. A long-term study and a larger number of samples are needed to evaluate the fate of this autophagic accumulation.

**The Role of Antibodies in Pompe Disease**

Priya Kishnani, M.D.
Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme acid alpha-glucosidase. It represents a clinical spectrum -infantile Pompe disease at one end, which is rapidly progressive with death in the first year of life to adults with the condition that can present as late as the seventh decade at the other extreme. Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme-) has improved the prognosis of individuals with Pompe disease with improved survival and quality of life. There is however a subset of patients that have an inadequate clinical response to ERT. Factors impacting outcome include age at onset, stage of the disease, muscle fiber type, defective autophagy, underlying Cross reacting immunological material (CRIM) status and presence of high sustained antibody titers (HSAT). A systematic study by our group has shown that there is a significant difference in clinical outcome in patients with HSAT versus patients that have tolerized or have low sustained antibody titers (LSAT) to Myozyme. Immune modulation therapies have been developed to combat the immune response for patients at risk or those who have developed HSAT to Myozyme- ERT. With the advent of these therapies, identification of patients at risk for developing high sustained antibody titer (HSAT) is critical. We have a system in place to identify individuals at risk for HSAT prior to start of ERT which allows for early treatment intervention with immune tolerance induction (ITI) protocols. ITI protocols using rituximab, methotrexate and intravenous immunoglobulin (IVIG) have been successful with a good clinical response when initiated in the naive setting or early in the immune response. These strategies have failed to combat the immune response in patients with HSAT. A reason is the lack of agents in ITI protocols that target plasma cells, the long lived cells that are the source of antibody production. We will present our experience with agents that target plasma cells, in combination with rituximab, methotrexate and IVIG in patients with HSAT. The treatment regimen has been well tolerated with no side effects and the clinical response has been very good.

We will discuss the current challenges of antibody titers in Pompe patients on ERT, the need for early identification of patients at risk and treatment approaches that have resulted in good outcome. Future directions will also be discussed.

**Muscle Regeneration**

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

Pompe disease is a lysosomal storage disorder caused by the deficiency of acid alpha-glucosidase. Deficiency of alpha-glucosidase leads to glycogen storage mainly affecting skeletal muscles. In infantile Pompe disease progressive storage of glycogen is observed in virtually all muscle cells leading to destruction of muscle fibres and a fast progressive generalized muscle weakness. In patients with late onset Pompe disease glycogen storage is more variable, while the limb girdle muscles are affected most. Differences in the residual level of alpha-glucosidase and the type of mutations in the alpha-glucosidase gene largely explain the differences in disease course between infants and adults with Pompe disease.

Skeletal muscle is the most abundant tissue of our body. During growth and the gradual transition from infancy to adulthood skeletal muscle mass increases dramatically and composes during adulthood 40-50% of the human body, while after the age of 45-50 years muscle mass starts to decrease again. Apart from its essential role in locomotion, skeletal muscle is also the body’s main store of carbohydrate and protein as well as being one of the principal generators of heat. Its proper maintenance and function are, therefore, essential.

During the lecture issues will be addressed that relate to muscle growth, muscle damage and regeneration in Pompe disease.
Pre-clinical Studies of Gene Therapy for Pompe Disease
Andrea Amalfitano, D.O., Ph.D.
Department of Microbiology and Molecular Genetics, Michigan State University

Our group has pioneered research into the potential to treat Pompe patients via gene transfer based therapeutics. Early in our studies we found that direct intramuscular transfer of the acid alpha glucosidase (GAA) gene via Adenovirus (Ad) or Adeno-Associated Virus (AAV) based vectors could result in localized expression of GAA, as well limited secretion of GAA protein from the so-treated muscles. However, the amounts of GAA protein secreted from these few cells was not able to correct distant muscles not directly injected with the gene transfer vector. This enormous limitation pushed our group to use Gene Transfer Technologies in a manner that can allow for correction of potentially ALL the affected muscles in a Pompe patient. In fact, we first confirmed that a simple, intravenous delivery of gene transfer vectors resulted in high level transfer of the GAA gene into the liver. The liver, being a natural secretory organ, sustained hepatic GAA protein secretion into the blood stream of so treated animals over long periods of time. Glycosylation and secretion of the liver produced GAA allowed for efficient and widespread muscle cell uptake of GAA throughout the animal’s body, resulting in long-term correction of glycogen storage in multiple muscle groups of both quail and murine models of Pompe disease. Furthermore, our studies verified for the first time that muscle strength could be improved rapidly, as well preserved long after the initial injection of the gene transfer vector occurred. These studies further confirmed the importance that genetic background differences amongst Pompe patients likely have relative to generation of adaptive immune responses to GAA, verifying results noted in human clinical trials utilizing recombinant GAA in Enzyme Replacement Therapy based strategies. We now need to prove that our observations in small animal models using intravenous delivery of GAA expressing gene transfer vectors can be replicated in large, non human primate models. We have recently initiated baboon based gene therapy models as a prelude to human clinical trials. We have constructed a fully deleted (FD) Ad vector expressing the simian (baboon) version of the GAA gene (FDAd-bGAA). This approach will minimize the potential generation of antibodies to the vector delivered bGAA gene, fostering the potential for longer-term efficacy in this animal model. With our collaborator, Dr. Philip Ng, (Baylor College of Medicine, Houston, Texas) we will utilize a novel, balloon occlusion and catheter mediated technique for isolated delivery of FDAdS into the baboon liver, allowing for safer, more efficacious GAA gene delivery into the liver, at relatively low vector doses.


Treatment Strategies for Pompe Disease: Lessons from Preclinical and Clinical Studies
Barry J. Byrne, M.D., Ph.D.
Department of Pediatrics and Powell Gene Therapy Center, University of Florida

Pompe disease, due to partial or complete loss of alpha-glucosidase activity, is a complex disease process due to glycogen accumulation and cellular dysfunction in all cell types. Cardiopulmonary dysfunction is the most early life threatening complication and contributes to death in the first year of life. The profound weakness observed in early onset or severe Pompe disease has been attributed primarily to dysfunction of muscle cells. Recent findings and ongoing observations in clinical studies have revealed a new natural history of the disease in those with early onset disease. The most notable development in subjects receiving enzyme replacement therapy is the progressive loss of independent ventilation. Further evaluation of preclinical models of Pompe disease has revealed that the principal cause of respiratory insufficiency is motor neuron dysfunction. To address the deficits in motor neuron and muscle dysfunction, a gene therapy approach has been used to target these two target tissues. Three strategies to reverse the impact of alpha-glucosidase deficiency have been evaluated, including enzyme replacement therapy using multiple receptor targets, pharmacological chaperones and AAV-mediated gene replacement therapy. The early results of the first clinical gene therapy study in Pompe will be emphasized. In addition to the novel modes of action for each of these therapeutic strategies there are important opportunities for combined therapy in the future.
Enhancement of Gene Therapy in Pompe Disease by Increased Mannose-6-Phosphate Receptor Expression in Target Tissues
Dwight D. Koeberl1*, Baodong Sun1, Jian Dai1, Songtao Li1, Andrew Bird1, and Deeksha S. Bali1.
1Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center

The underlying deficiency of acid α-glucosidase (GAA) in Pompe disease has been partially corrected by enzyme replacement (ERT). However, skeletal muscle weakness persists in many patients on ERT, and poor uptake of GAA by skeletal muscle has been linked to low abundance of the cation-independent mannose-6-phosphate receptor (CI-MPR). To further understand the role of CI-MPR in Pompe disease, we crossed muscle-specific CI-MPR knockout (KO) mice with GAA-KO (Pompe disease) mice. We evaluated adeno-associated virus (AAV) vector-mediated gene therapy in CI-MPR-KO/GAA-KO (double KO) mice. The essential role of CI-MPR was emphasized by the lack of efficacy from AAV vector administration, as demonstrated by markedly reduced biochemical correction of GAA deficiency and of glycogen accumulations in double KO mice, in comparison with administration of the same AAV vector in GAA-KO mice. We next attempted to increase CI-MPR expression in skeletal muscle to demonstrate the dependence of biochemical correction upon receptor-mediated uptake of GAA. Therefore, the AAV vector-transduced liver depot was enhanced by the addition of a drug, clenbuterol, which was previously demonstrated to increase the expression of CI-MPR in muscle. The liver was transduced by administering AAV-LSPHGAapA (2×1010 vector particles) to two groups of 3 month-old male GAA-KO mice, and clenbuterol was administered to one group of vector-treated mice. The effect of clenbuterol was evident, when Rotarod latency was increased by 75% following vector administration and clenbuterol treatment, in comparison with vector administration alone (p=2×10−5). The efficacy from clenbuterol treatment was evaluated with regard to biochemical correction of GAA deficiency and glycogen storage in striated muscles and the brain. GAA activity was significantly increased in the heart following vector administration and clenbuterol treatment, in comparison with vector administration alone (p=0.03). Glycogen content was reduced in the diaphragm (p=0.04), soleus (p=0.006), extensor digitorum longus (EDL; p=0.002), cerebrum (p=5×10−6), and cerebellum (p=0.03) following vector administration and clenbuterol treatment, in comparison with vector administration alone. The basis for increased glycogen clearance during clenbuterol treatment was demonstrated by Western blotting detection of CI-MPR. The signal for CI-MPR was increased in the EDL (p=0.05) and cerebrum (p=0.01) of clenbuterol-treated GAA-KO mice. Furthermore, the effect of gene therapy with clenbuterol enhancement was evaluated in 15 month-old female GAA-KO mice, because elderly, female mice with Pompe disease are particularly resistant to correction with AAV vector-mediated gene therapy. Significantly increased Rotarod latency (p=0.02) and weight (p=0.04) were demonstrated 12 weeks following the initiation of therapy, indicating that long-term efficacy had been achieved in advanced Pompe disease. In summary, enhanced CI-MPR expression might improve the efficacy from gene therapy in Pompe disease through enhancing receptor-mediated uptake of GAA, and gene therapy could be similarly enhanced in other lysosomal storage disorders that primarily involve the brain.

Lentiviral Hematopoietic Stem Cell gene therapy for Pompe disease
Merel Stok1, Helen de Boer1, Trudie P. Visser1, Arnold J.J. Reuser2, Ed.H. Jacobs1, Holger Jahr4, Elza D. van Deel1, Dirk J. Duncker2, Niek P. van Tiel1 and Gerard Wagena1
1. Erasmus University Medical Center, Department of Hematology, Rotterdam, the Netherlands. 2. Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, the Netherlands. 3. Erasmus University Medical Center, Department of Genetics, Rotterdam, the Netherlands. 4. Erasmus University Medical Center, Department of Orthopedics, Rotterdam, the Netherlands. 5. Erasmus University Medical Center, Department of Experimental Cardiology, Rotterdam, the Netherlands

Pompe disease, caused by mutations in the gene encoding acid alpha-glucosidase (GAA), currently lacks a single intervention therapy with curative intent. Enzyme replacement therapy is an effective treatment modality, but is not beneficial to all patients, may result in antibodies against the recombinant enzyme and the costs are high. We have explored in a Gaa−/− mouse model the development of an ex vivo lentiviral vector mediated hematopoietic stem cell gene therapy strategy aiming at sustained systemic production of GAA by a small fraction of the blood cell production system. Using this strategy, life-long high levels of (human) alpha-glucosidase were achieved in leukocytes and all affected tissues of Pompe mice using relatively mild conditioning, with the spleen focus forming virus (SF) promoter driving the used GAA sequence. Supranormal levels of GAA activity were obtained in all affected tissues, including skeletal muscle, consistent with an almost complete reduction of glycogen storage. Heart morphology and function as well as skeletal muscle function normalized, while reduction of glycogen to near normal levels was found in brain and cartilage. Adverse effects of the approach on blood cell production were not observed during prolonged monitoring of the Gaa−/− mice. We conclude that ex vivo hematopoietic stem cell lentiviral vector mediated gene therapy results in correction of the Pompe phenotype in the Gaa−/− mouse model. Ongoing research is directed at its further development towards clinical implementation.
A Special Thanks to Our Silver Level Sponsor:

A Special Thanks to Our Bronze Level Sponsor:
A Special Thanks to Our Gold Level Sponsor:

enzyme
A SANOFI COMPANY
Thank You for Coming!

DVDs of the Conference will be made available for purchase. Stay tuned to the AMDA website (amda-pompe.org) for more information.