Welcome!

2019 AMDA/IPA
International Pompe Patient and Scientific Conference
# Table of Contents

- Introduction: Page 5
- Helpful Tips and Information: Page 6
- Conference Agenda: Page 7
- Speaker Biographies: Pages 8-15
- Abstracts: Pages 16-23
- Acknowledgements: Pages 24-26
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 2019 AMDA/IPA Pompe Patient and Scientific Conference!

I am very excited to announce that we are expecting around 200 Conference participants from 15 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-four (24) years the AMDA has seen a treatment for Pompe disease become a hope, and then a reality. Gene therapy, next generation ERTs, and stem cell therapy 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. One thing is clear—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.

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 Speakers on their material for this Brochure. Her help and support have been indispensable.

Thank you Marsha!
Helpful Tips and Information

**General Information**

All presentations and meals during 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.

**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

**A Chance to Say Thank You!**

In 2011 the PCMA of Texas hosted the first annual Pull for Pompe. All proceeds from this fundraiser have gone to support the annual AMDA Research Grant. Thanks to the support of the PCMA, over $1.3 Million Dollars has been donated directly to researchers working on Pompe Disease research so far. Many of the Grant Recipients will be presenting at the Conference this weekend.

The 10th Annual Pull for Pompe will take place in April 2020. The AMDA will be preparing a short video to share with the PCMA of Texas to thank them for their on-going support of our Community. Without their support, we would never have been able to support all of the research we have supported.

If you would like to be included in the video and say “Thank You” to the PCMA, please take a moment during a break or meal and stop by Bolero 2!
Conference Agenda
October 25, 2019 – October 27, 2019
San Antonio, Texas

FRIDAY, OCTOBER 25TH, 2019
Conference Registration
1:00-5:30
Lobby of the Holiday Inn Riverwalk
Welcome Dinner
6:00-9:00
(Buses depart from the Lobby of the Holiday Inn at 6 PM)

SATURDAY, OCTOBER 26TH, 2019
Breakfast
7:00-8:00
Welcome Address
8:00-8:10
Crash Course in Pompe
8:10-8:40
Dr. Arnold Reuser (Erasmus University)

Natural History vs New History with Treatment
Chair: Dr. Pascal Laforêt
Natural History vs New History: Infantile-Onset
Dr. Priya Kishnani (Duke University)
Natural History vs New History: Late-Onset
Dr. Ans van der Ploeg (Erasmus University)
Newborn Screening: Taiwan Experience
Dr. Yin-Hsiu Chien (National Taiwan University Hospital)
Question and Answer
9:40-10:00
Break
10:00-10:20
Integrative Care of Pompe Patients
Dr. Hannerieke van den Hout (Erasmus University)
Question and Answer
10:20-10:50
The Basics of Clinical Trials
Chair: Dr. Priya Kishnani
Clinical Trial Relate Issues for Pompe Disease
Dr. Benedikt Schosser (Friedrich-Baur-Institute)
Patient Perspective on Clinical Trials
Ryan Colburn (United States)
Patient Organization View on Clinical Trials
Ria Broekgaarden (IPA, VSN)
Question and Answer
11:55-12:00
Lunch
12:00-1:00
Management and Care of Pompe Patients
Chair: Dr. Ans van der Ploeg
Improved Muscle Function in a Phase I/II Clinical Trial of Albuterol in Pompe Disease
1:00-1:20
Dr. Dwight Koeberl (Duke University)
Exercise and Nutritional Considerations for the Treatment of Pompe Disease
1:20-1:40
Dr. Mark Tamopolsky (McMaster University)
Respiratory Muscle Training in Late-Onset Pompe Disease: Randomized Controlled Trial Results
1:40-2:00
Dr. Hamison Jones (Duke University)
Noninvasive Respiratory Management of Pompe Disease
2:00-2:20
Dr. John Bach (Rutgers University)
Question and Answer
2:20-2:40
Break
2:40-3:00
Expert Round Table: 20 Years of Treatment and Care
Chair: Tiffany House (IPA, AMDA)
Dr. Pascal Laforêt (Versailles-Saint Quentin University)
3:00-3:10
Dr. Priya Kishnani (Duke University)
3:10-3:20
Dr. Benedikt Schosser (Friedrich-Baur-Institute)
3:20-3:30
Dr. Ans van der Ploeg (Erasmus University)
3:30-3:40
Open Discussion with Audience
3:40-4:30
Break
4:30-4:45

SUNDAY, OCTOBER 27TH, 2019
Breakfast
7:00-8:00
Next Generation Therapy: Enzyme Replacement Therapy (ERT)
Chair: Dr. Nina Raben (NIH)
How Enzyme Replacement Therapy Works
8:00-8:10
Update on Amicus Trials with ERT Associated with Chaperone Molecule
Dr. Pascal Laforêt (Versailles-Saint Quentin University)
Update on Genzyme’s Neo-GAA
8:25-8:40
Dr. Benedikt Schosser (Friedrich-Baur-Institute)
Preclinical studies for Oral-ERT with a Tobacco Seed-Derived a Recombinant Acid Maltase
8:40-8:55
Dr. Frank Martinuk (JME Group)
Safety and Efficacy Data Using VAL-1221 in Patients with LOPD
8:55-9:10
Dr. Priya Kishnani (Duke University)
Question and Answer
9:10-9:30
Break
9:30-9:50
Next Generation Therapy: Gene Therapy
Chair: Arnold Reuser (Erasmus University)
Basics of Gene Therapy
9:50-10:00
A Phase 1 Study of the Safety of AAV8-LSPhGAA (ACTUS-101) in Late-Onset Pompe Disease (LOPD)
10:00-10:15
Dr. Dwight Koeberl (Duke University)
Lentiviral Gene Therapy and Antisense Oligonucleotides for Pompe Disease
10:15-10:30
Dr. Pim Pijnappel (Erasmus University)
AAV-Mediated Gene Therapy in Pompe Disease: Clinical Immunology
10:30-10:45
Dr. Barry Byrne (University of Florida)
Gene Therapy for Pompe Disease: From Bench to Bedside
10:45-11:00
Dr. Giuseppe Ronzitti (Genethon-France)
Question and Answer
11:00-11:20
Break
11:20-11:40
Future Research
Chair: Benedikt Schosser (Friedrich-Baur-Institute)
Skeletal Muscle Abnormalities in Pompe Disease Can Be Reversed by Enzyme Replacement Therapy
11:40-12:00
Dr. Nina Raben (NIH)
The Common c.-32-13T>G Splicing Variant of GAA Gene: From Functional Characterization to the Identification of New Therapeutic Targets for Pompe Disease
12:00-12:20
Dr. Andrea Dardis (Regional Coordinator Centre for Rare Diseases, Udine)
Targeting Glycogen Synthase (GYS1) with Antisense Oligonucleotide Treatment in a Mouse Model of Pompe Disease
12:20-12:40
Dr. Virginia Kimonis (University of California-Irvine)
Stem Cell and Muscle Regeneration in Pompe
12:40-1:00
Dr. Pim Pijnappel (Erasmus University)

END OF DAY ONE

IPA/Erasmus Survey and Pompe Registry
Chair: Thomas Schaller (IPA, Pompe Germany)
The IPA/Erasmus Pompe Survey: Past, Present, and Future
4:45-5:00
Dr. Nadine van der Beek (Erasmus University)
Report from Genzyme’s Pompe Registry
5:00-5:15
Dr. Virginia Kimonis (University of California-Irvine)
Question and Answer
5:15-5:30
PATIENT MIXER
7:00-9:00
Skyline Atrium of the Holiday Inn Riverwalk

CONFERENCE CLOSE
John Bach, M.D. (Rutgers University)

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 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 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 7 medical textbooks on neuromuscular and pulmonary medicine and has lectured on these topics in 65 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.

Ria Broekgaardan (Vereniging Spierziektten Nederland, International Pompe Assoc.)

Ria is a project leader for Spinal Muscular Atrophy (SMA) and Pompe Disease at Vereniging Spierziektten Nederland (VSN), a Dutch Neuro Muscular Disease Patient organization. She is also involved with Facioscapulohumeral muscular dystrophy (FSHD) and Muscular Dystrophy (MD) at the VSN. In addition, Ria is a founder of the International Pompe Association (IPA) and continues to serve as an adviser to the IPA. Ria is also a former FSHD board member and a Founder of FSHD Europe. She has experience in drug development from the first development to availability (Pompe/SMA). She went through all stages and had to deal with supply and reimbursement issues, negative press, small/broad label, start stop criteria etc in Pompe Disease.

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

Dr. Barry Byrne is a clinician scientist who is studying a variety of rare diseases with the specific goal of developing therapies for inherited muscle disease. As a pediatric cardiologist, his focus is on conditions that lead to skeletal muscle weakness and abnormalities in heart and respiratory function. His group has made significant contributions to the understanding and treatment of Pompe disease, a type of neuromuscular disease due to glycogen storage in motor units. The research team has been developing new therapies using AAV-mediated gene therapy to restore cardiac and skeletal muscle function in DMD, Friedreich’s ataxia, Pompe, and other inherited neuromuscular diseases. His group at the Powell Center has also established a series of new methods for large-scale AAV clinical manufacturing. The work is supported by several NIH and foundation awards.

Dr. Byrne is the Associate Chair of Pediatrics and Director of the University of Florida Powell Center and Child Health Research Institute. He obtained his B.S. degree from Denison University; M.D. and Ph.D. from the University of Illinois; and he completed his Pediatrics residency and cardiology fellowship as well as post-doctoral training in Biological Chemistry at the Johns Hopkins Hospital. Following his early career at Hopkins, he joined the University of Florida and is now the Earl and Christy Powell University Chair in Genetics.

In addition to his academic appointments, he serves as the Chief Medical Advisor of the Muscular Dystrophy Association and a member of the TACT committee of TREAT-NMD. He is an advisor to the Pfizer Rare Disease Therapeutic Area Advisory Committee and co-founder of AavantiBio.
Yin-Hsiu Chien, M.D., Ph.D. (National Taiwan University Hospital)

Dr. Yin-Hsiu Chien is a Clinical Professor at the Department of Pediatrics at the National Taiwan University in Taipei, Taiwan, and Attending Physician of the Department of Medical Genetics and Pediatrics at the National Taiwan University Hospital. She graduated from Chang-Gung Medical School, undertook pediatric residency training at the National Taiwan University Hospital, and obtained her Ph.D. from the National Taiwan University. Dr. Chien has made diverse contributions in the field of inborn errors of metabolisms and immunodeficiency, publishing over 50 original research articles in the last 5 years. She is Director of the newborn screening center at the National Taiwan University Hospital, which routinely screens around one-third of newborns in Taiwan. Her team, led by Dr. Wuh-Liang Hwu, is devoted to the diagnosis and treatment of lysosomal storage diseases, neurotransmitters deficiency, and neuromuscular disorders. Dr. Chien’s current work focuses on early diagnosis and improvement of treatment for Pompe disease, AADC deficiency, Spinal muscular atrophy, and other LSDs.

Ryan Colburn (Pompe Patient – United States)

Ryan Colburn is a rare disease patient with a professional background in engineering and operations management; spending portions of his career working on race cars, airplanes, and rockets. Diagnosed with Pompe disease in 2015, he has spent the time since learning about rare disease topics including research, advocacy, and drug development to better understand how to participate in the rare disease ecosystem. He is passionate about patient empowerment and engagement; actively developing relationships with other patients, advocacy groups, researchers, and pharmaceutical companies. He is driven to find the most effective ways to tackle the challenges of rare disease and break down barriers to the acceleration of progress.

Andrea Dardis, Ph.D. (Regional Coordinator Centre for Rare Diseases, Udine, Italy)

Dr. Andrea Dardis is Head of the Laboratory of the Regional Coordinator Centre for Rare Diseases, Udine, Italy.

She obtained her PhD in molecular biology at the University of Buenos Aires, Argentina and continued her training at the Metabolic Unit, University of California, San Francisco, USA as a post-doctoral fellow. During her training she was awarded Fellowship of the Lawson Wilkins Pediatric Endocrine Society. She then moved to Italy where she got a Specialist Degree in Medical Genetics at the University of Genoa.

In 2003 she joined the Metabolic Diseases Unit, Pediatric Hospital “Burlo Garofolo”, Trieste, Italy, as a Research Scientist. In 2009 she moved to the Regional Coordinator Centre for Rare Diseases in Udine, Italy, where she became Head of the lab. Dr. Dardis Laboratory activities are mainly focused on the biochemical and molecular diagnosis of lysosomal storage diseases, the functional characterization of defective lysosomal enzymes and the study of molecular mechanisms involved in the pathogenesis of lysosomal storage disorders.

She is the author of more than 80 research papers in peer-reviewed publications and of book articles on these subjects. She is the Academic Editor at PloS ONE, Board Member of the European Working Group of Gaucher Disease (EWGGD) and Trustee for the International Niemann Pick Disease Registry (INPDR).

Fabio Di Pietro (Pompe Patient – Italy)

Fabio Di Pietro is a 41-year-old from Sicily, Italy. In 2015, he participated in the first edition of the IPA Pompe Empowerment Program in the Netherlands. The program was designed to train new Pompe patient advocates and gave Fabio the opportunity to learn from inspirational patient leaders the skills to become involved with patient advocacy. Since then Fabio has engaged in national and international patient advocacy activities. In 2017 Fabio joined the Board of the International Pompe Association (IPA). With the IPA, among other activities, he has been involved with International Pompe Day awareness campaigns, and with the organization of the newly established Community Advisory Board. He is also a member of AIG, the Italian Association for Glycogen Storage Disease.
**Harrison Jones, Ph.D. (Duke University Medical Center)**

Dr. Harrison Jones, Ph.D., is an Associate Professor in the Department of Head and Neck Surgery & Communication Sciences at the Duke University School of Medicine. Dr. Jones’ research interests include respiratory muscle training (RMT), measurement of lingual function and structure, communication and swallowing disorders, and surveillance of children identified with late-onset Pompe disease identified via newborn screening. He was Principal Investigator (PI) for a recently completed exploratory, sham-controlled clinical trial of RMT in late-onset Pompe disease funded by NIH NIAMS. He is also PI for a Sanofi Genzyme-sponsored study to determine the diagnostic utility of measures of lingual function and structure in LOPD. Dr. Jones has recently submitted two U.S. patent applications for novel RMT technologies, one of which has been licensed and commercialized by Aspire as the Inspiratory Adapter 150.

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

Dr. Kimonis is currently a clinician Scientist and tenured professor in the Division of Genetics and Genomic Medicine, Department of Pediatrics, UC Irvine, and Children’s Hospital, Orange County. Dr. Kimonis received her medical degree from Southampton Medical School, United Kingdom and trained in pediatrics and general practice in the UK before moving to the US. She completed a residency in 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, Clinical and Biochemical Genetics. She previously served as the Chief of Genetics at Southern Illinois University School of Medicine. She worked at Boston Children’s Hospital/Harvard Medical School before joining UC Irvine in 2006 as the Chief of the Division of Genetic Medicine and Genomic Medicine until 2012.

Dr. Kimonis’ clinical interests are varied. She participates in comprehensive service in Clinical and Biochemical Genetics. She specializes in the diagnosis and management of children and adults with neuromuscular, neurodegenerative, dysmorphic features, and other complex disorders. Dr Kimonis is an active tutor and lecturer and teaches genetics fellows, residents, and medical students, genetic counseling graduate and undergraduate students. Additionally, she mentors postdocs and other trainees in their laboratory projects.

She has an active clinical research and laboratory program that primarily focuses on inherited muscle disorders, lysosomal storage diseases, Prader Willi, as well as several other rare disorders. She has developed the University of California, Irvine Lysosomal Disease Program, and conducts a registry study in a large cohort of patients with Pompe disease. She completed a trial of resistance training for axial and respiratory muscles in Pompe disease as an adjunct to enzyme replacement treatment. She discovered an important disease: multisystem proteinopathy associated with mutations in the VCP gene, which has overlap with Pompe disease. She has received funding from the NIH, MDA, Paget Foundation, AMDA, hiIBM and other foundations for her research. Dr. Kimonis’ goal is to integrate the basic science research with clinical research, establish a premier clinical, and research program in Rare Genetic Diseases.

**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, gene therapy and small molecules. She has propelled a translational research program at Duke with a T1-T4 impact, implementing bench-to-bedside approach, and from the bedside back to the bench for further advances toward the diagnosis, treatment and management of patients with rare genetic diseases.

Dr Kishnani has built an interdisciplinary team whose efforts are most notably demonstrated by the long-standing research and clinical experience that resulted in FDA approval of alglucosidase alfa (Myozyme™) as the only available treatment for Pompe disease in 2006.
Dwight Koeberl, M.D., Ph.D. (Duke University Medical Center)

Dr. Koeberl attended Carleton College, and then 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. He serves as Medical Director for the Pediatrics Biochemical Genetics Laboratory and sees patients in the Metabolic Clinic. At Duke his research has focused upon the development of new therapy for inherited metabolic disorders, especially for the glycogen storage diseases. He was recruited to Duke by Dr. Y-T Chen, who developed enzyme replacement therapy for Pompe disease. Dr. Koeberl is currently developing drug and gene therapy for Pompe disease.

Professor Pascal Laforêt, M.D., Ph.D. (Versailles-Saint Quentin University, France)

Pascal Laforêt, MD, PhD, is a professor of Neurology at the Versailles-Saint Quentin University, consultant specialized in neuromuscular disorders (myasthenia gravis, muscular dystrophies, and metabolic myopathies) in the Neurology department of Raymond-Poincaré hospital, and coordinator of Nord/Est/Ile de France neuromuscular center. He is a member of the U1179 INSERM-UVSQ laboratory, dedicated to biotherapies of neuromuscular system diseases. The major focus of his research activities is metabolic myopathies (pathophysiology and clinical trials), and he coordinates the French registries for mitochondrial disorders, glycogenosis type III, and Pompe disease. He is a member of the European NeuroMuscular Center (ENMC) research committee, French Myology Society (SFM), scientific committees of the French Association against Myopathy (AFM) and French Glycogenosis association (AFG).

Frank Martiniuk, Ph.D. (JME Group)

Presently, Dr. Martiniuk serves as the Vice-President of Research at JME Group. He received his Ph.D. in biology from NYU. He had his own independent research laboratory and was the Director of the Molecular Corelab in the General Clinical Research Center or Clinical Translational Science Institute (CTSI) at NYU School of Medicine. He has obtained 24 grants as a Principal Investigator (PI) from NIH and private foundations, including grants on gene therapy, and has served as a reviewer for many journals and grants. He has been studying GAA and Pompe disease for over forty years. Briefly, he studied the biochemistry and genetics of acid maltase plus established many cell lines. He isolated the first authentic GAA gene and determined the mutations for over 150 patients. Additionally, he estimated the number of affected individuals in the USA by a molecular survey of mutations in the general population and has been evaluating treatment of Pompe disease by non-viral gene and enzyme replacement therapies. As the director of the CTSI, he was involved in a wide range of clinical and basic research studies including investigations in viral and non-viral gene therapy from design, preparation of reagents and analyses/PK of in vitro and in vivo experiments. He has been studying the heat shock 65 gene and protein from Mycobacterium leprae and has identified novel RFLPs for the gene that is used in the molecular epidemiology of leprosy. He is confirming the genome sequence for the newly discovered and lethal strain of leprosy- M. lepromatosis. Additionally, he has bio-statistical education/training at NYUSoM medical statistics, and the CTSI-bio-statistics course.

Kevin O'Donnell, Ph.D. (International Pompe Association-Scotland)

Dr. Kevin O'Donnell is based in Edinburgh, Scotland. Although a professional scientist, his interest in Pompe disease is personal; he and his late 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, www.pompestory.blogspot.com.

He recently took early retirement from science to refrain as a counsellor/psychotherapist and is in the final year of his Masters at the University of Edinburgh. He says: "I finally realized I was more interested in people than plants."

Kevin and his late wife Elaine also have two children not affected by Pompe disease.
Pim Pijnappel, Ph.D. (Erasmus University Medical Center-The Netherlands)

Dr. W.W.M. (Pim) Pijnappel is an Associate Professor at the Center for Lysosomal and Metabolic Diseases, Erasmus MC, The Netherlands, where he heads a basic and translational research group on lysosomal storage diseases, with a focus on Pompe disease and Mucopolysaccharidoses. He has broad expertise in cell and molecular biology and received training at the Hubrecht laboratory (Utrecht) and European Molecular Biology Laboratory (Heidelberg). He has published in top journals including Nature, Cell, Genes and Development, Nature Biotechnology, and PNAS. He is Board Member of the Center for Lysosomal Diseases at the Erasmus MC, member of the indication committee of the Erasmus MC which decides on treatment of Pompe disease with enzyme replacement therapy, and treasurer of the European Study Group of Lysosomal Disorders. His research group works on the development of novel therapeutic approaches for lysosomal diseases including stem cell-based gene therapy and antisense oligonucleotides, improved diagnostics, molecular mechanisms of disease and the effects of enzyme replacement therapy. This has resulted in numerous publications and patents.

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

Dr. 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. Since the 1990s, she has been working on inflammatory and metabolic myopathies at the National Institutes of Health. The major focus of her research is a genetic disorder caused by a deficiency of lysosomal enzyme acid alpha-glucosidase (GAA), known as glycogen storage disease type II or Pompe disease. She has published over 100 peer-reviewed papers on the subject. The studies include mutational analysis of the gene and development of several knockout and transgenic mouse models of Pompe disease (one of these mouse models has become the principal tool throughout the world for the Pompe studies); generation of conditionally immortalized myogenic WT and GAA-KO cell lines; investigation of the role of autophagy in the pathogenesis of the disease; identification of mTOR kinase and transcription factors as potential therapeutic targets; and extensive pre-clinical studies with Myozyme/Lumizyme and a recently developed new experimental recombinant human GAA for enzyme replacement therapy for Pompe disease.

Arnold Reuser Ph.D. (Erasmus University Medical Center-The Netherlands)

Dr. Arnold Reuser studied chemistry at the University of Amsterdam and graduated in biochemistry in 1973. He became Lecturer at the Medical Faculty of the University of Rotterdam, later called Erasmus MC University Medical Centre. There he obtained his Ph.D. degree in 1977 with a thesis on the Clinical, Biochemical and Genetic Heterogeneity in Pompe disease and related lysosomal storage disorders.

As young ‘postdoc’ -Research Associate at the Institute for Cancer Research, Fox Chase, Philadelphia, USA- he pioneered the development of mouse models for human genetic diseases in the laboratory of Dr. Beatrice Mintz. In 1980, he continued his career at Erasmus MC where he became head of the Lysosomal Study Group and professor in Cell Biology and Histology. His research interests remained focused on Pompe disease.

Research by the team members of the ‘pompecenter’ at Erasmus MC, Rotterdam, The Netherlands, has led to the cloning of the GAA gene, the making of the first mouse models of Pompe disease, the production of recombinant human GAA in CHO cells and milk of transgenic mice and rabbits, and ultimately to enzyme replacement therapy for Pompe disease.

Profs. Ans van der Ploeg and Pim Pijnappel are currently heading the ‘pompecenter’ at Erasmus MC-Sophia Children’s Hospital and the Department of Clinical Genetics, Rotterdam, the Netherlands. www.pompecenter.nl
Giuseppe Ronzitti, Ph.D. (Genethon-France)

Giuseppe Ronzitti was born in Italy. He received his Biotechnology degree from the Modena University and his Ph.D. in Biochemistry from the Bologna University.

After a post-doc in molecular neuroscience, in 2013 he joined the team of Dr. Mingozzi at Genethon. In this position, he was involved in the pre-clinical evaluation and optimization of an AAV-based treatment for the Crigler-Najjar syndrome that is now in the clinic (NCT03466463). He also participated in the development of a liver-targeted gene therapy for Pompe disease.

In 2015 he was awarded with a Marie Curie Sklodowska Fellowship for the development of a proof of concept for the treatment of GSDIII. Since then his research has been focused on the development of AAV gene therapy approaches for metabolic diseases of genetic origin.

Dr. Ronzitti published 29 original research manuscripts with a cumulative impact factor of 180 that received more than 800 citations. He also contributed to six review articles, four book chapters and four commentaries. Importantly, Dr Ronzitti authored more than ten patents on the development of AAV-based gene therapy strategies.

Dr. Ronzitti is now a tenured researcher at INSERM, one of the biggest research institutes dedicated to biomedical research and human health in the world. He is also team leader at Genethon, a non-profit institute devoted to the development of gene therapy strategies for rare genetic diseases.

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

Dr. Benedikt Schoser started his career with training in muscle pathology by Hans Goebel and finishing his medical thesis at the Institute of Neuropathology in Mainz, Germany in 1993.

He started his career in neurology at the University Hospitals Mainz, Frankfurt, and Hamburg, Germany, in 1993, where he was trained in general neurology, intensive care neurology, psychiatry, and clinical neurophysiology. After spending a year in Thomas Jentsch’s laboratory at the Institute of Neuropathophysiology in Hamburg, he was nominated as fulltime senior neurologist in 2001 at the Friedrich-Baur-Institute, Department of Neurology, Ludwig-Maximilians-University Munich. Additionally, in 2016 he received his diploma in palliative medicine. He received his post-graduate degree (Habilitation) from Ludwig-Maximilians-University Munich in 2004.

He is currently senior consultant neurologist and co-chair of the Friedrich-Baur-Institute, the major national referral center for rare neuromuscular diseases in Germany. At the Friedrich-Baur-Institute, they have established a large clinical trial unit and a large collection of biomaterial from neuromuscular patients including Myotonic Dystrophy types 1 and 2, non-dystrophic myotonia, several limb girdle dystrophies, myasthenic disorders, and metabolic myopathies.

Dr. Schoser has authored and co-authored more than 230 articles in peer reviewed journals and contributed more than 25 chapters to books on neurology and muscle pathology, mainly in the field of diagnostic features and translational therapeutic trials in myotonic dystrophies, muscular dystrophies, myasthenic syndromes, and metabolic myopathies including Pompe disease.

Dr. Schoser serves as member of the Editorial Board of Neuromuscular Disorders, Journal of Neuromuscular diseases. Dr. Schoser is co-founder and chair of the European Pompe consortium (EPOC). Since June 2016 he has served as co-chair of the Scientific Muscle and Neuromuscular panel of the European Academy of Neurology (EAN). In 2018 he became a fellow of the European Academy of Neurology (FEAN).

The goal of Dr. Schoser’s research is to investigate the molecular mechanisms of muscle loss and weakness in patients at all ages. His special interest is translating basic mechanism into clinical reality.
Mark Tarnopolsky, M.D., Ph.D. (McMaster University-Canada)

Dr. Tarnopolsky is the Clinical and Research Director of the Corkins/Lammert Family Neuromuscular and Neurometabolic Clinic at McMaster University. He holds an endowed chair at McMaster Children’s Hospital and Hamilton Health Sciences Foundation in Neuromuscular Diseases and is a Professor of Pediatrics and Medicine. He has received the Dr. David Green Award from the Muscular Dystrophy Association in 2005, the Barsky Lectureship for Excellence in Mitochondrial Medicine in 2007 and the honor award from the Canadian Society for Exercise Physiology 2008, the McMaster Distinguished Alumni Award for Science in 2012, and the International Biochemistry of Exercise Honor Award in 2015. His research focuses on nutritional, exercise, pharmacological and genetic therapies for neurometabolic (primarily mitochondrial), neuromuscular, and neurogenetic disorders as well as diseases associated with aging.

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

Dr. Hannerieke van den Hout obtained her medical degree at the University of Maastricht, the Netherlands, in 1995. She undertook her Ph.D. research in Rotterdam, studying the first four patients worldwide with classic infantile Pompe disease to be treated with recombinant alpha-glucosidase from rabbit milk.

After her training in pediatrics and child neurology, she specialized as a child neurologist for neurometabolic and neuromuscular diseases. She currently works as a child neurologist and clinic supervisor in the Center for Lysosomal and Metabolic Diseases (CLMD) in the Erasmus MC/Sophia Children’s Hospital in Rotterdam, led by Prof. Ans van der Ploeg. In this Center pediatricians, pediatric neurologists, neurologists, internists, pharmacists, biochemists and basic scientists work closely together to improve the future for patients with Pompe disease.

Dr. van den Hout’s research interests mainly concern the neurologic consequences of lysosomal storage disorders. She led the group which first described the pattern of white matter abnormalities in the brain and its consequences for cognition. Currently, she and her group are working on the in-depth study of the consequences of classic Infantile Pompe disease and innovative treatments focused on the brain.

Dr. van den Hout has authored many publications on enzyme replacement therapy and Pompe disease.

Nadine van der Beek, M.D. (Erasmus University Medical Center-The Netherlands)

Dr. N.A.M.E. van der Beek is a neurologist at the Center for Lysosomal and Metabolic Diseases of the Erasmus MC University Medical Center in Rotterdam, the Netherlands. As a neurologist, she is involved mainly in the care for adolescent and adult patients with neuromuscular diseases, especially patients with Pompe disease or other metabolic myopathies. From 2004 onward, she has coordinated the nationwide, prospective study on Pompe disease in the Netherlands. In 2014, she was awarded the Jan Meerwaldt award of the Dutch Neurological Society for her thesis ‘Clinical features, disease course and effects of enzyme therapy in Pompe disease’.

Her current scientific work focusses on the long-term effects of enzyme-replacement therapy in children and adults with Pompe disease, and the development and validation of new outcome measures. In 2017, she was granted a fellowship in neuromyology, which allowed her to work for several months at the Institut de Myologie at the Pitié-Salpêtrière Hospital in Paris. She is a board member of the European Pompe Consortium (EPOC), leading the work-package on patient-reported outcomes (PROs), and co-chair of the muscle disease working group (metabolic myopathies) of the European Reference Network (ERN) for neuromuscular disorders (Euro-NMD). Furthermore, she is a member of the Belgian-Dutch neuromuscular study group, the World Muscle Society (WMS), and European and American Academy of Neurology (EAN and AAN).
Professor Ans van der Ploeg, M.D., Ph.D. (Erasmus University Medical Center-The Netherlands)

Professor Ans T. van der Ploeg M.D., Ph.D. is Chair of the Center for Lysosomal and Metabolic Diseases at the Erasmus MC University, Rotterdam, and chair of department for metabolic diseases of Leiden University Medical Center, the Netherlands. The Center for Lysosomal and Metabolic Diseases is a joint initiative of the departments of Pediatrics, (Child)Neurology, Internal Medicine, Clinical Genetics and Hospital Pharmacy. It aims to improve treatment, care and diagnosis of children and adults, to stimulate translational research, to provide education and to disseminate information. The center is a designated rare disease expert center for Pompe disease, Lysosomal storage disorders, hypophosphatasia, urea cycle defects and organic acidurias and Porphyria. It serves as the national reference center for treatment with enzyme replacement therapy of patients with MPS I, MPS II, MPS VI, NCL and Pompe disease. The research performed by the Center has an important focus on lysosomal storage disorders and in particular Pompe disease, and includes clinical research (long term effects of ERT, dosing, immunomodulation, patient reported outcome) as well as development of innovative therapies (Gene, RNA based and cell-based therapies) and implementation of next generation (enzyme) therapies. The Center has collaborated since 2002 with the International Pompe Association on the IPA survey. The Center is governor of the international Pompe mutation database www.pompecenter.nl. Van der Ploeg is vice-coordinator of the European Pompe Consortium (EPOC), metabERN and coordinator of the LSD subnetwork of metabERN, and member of EuroNMD (European reference network for Neuromuscular Disorders). She is a member of several scientific advisory boards, member of the council of the Society of the Study Group of Inborn Errors of Metabolism (SSIEM). She was Chair and organizer of the SSIEM symposium named “building bridges” held in the Doelen in Rotterdam in 2019, which was attended by more than 3000 participants from 86 countries. The symposium focused, in particular, on innovative therapies such as gene therapy, regenerative medicine, RNA based therapies and potential benefits from other fields.

Dr. van der Ploeg received her M.D. “with honors” in 1985 at the Erasmus University. From 1985 until 1989 she worked at the Department of Cell Biology and Clinical Genetics on the feasibility of enzyme replacement therapy in cellular models for Pompe disease. Since then she has been involved in the multiple steps leading to the development of enzyme replacement therapy: Cloning of the gene, biotechnological production of recombinant human alpha-glucosidase (the enzyme deficient in Pompe disease) in milk of transgenic mice and rabbits, and in CHO cells; development of a knock-out model for Pompe disease; feasibility studies in mice and finally the first clinical trial in infants; and later the international multicenter placebo controlled trial that showed effects of therapy in adults. The current work of the Center on implementation and development of new therapies builds on this experience. Dr. van der Ploeg has received several awards for her work such as “The Research award for young investigators” from Erasmus University Rotterdam, the “Pharming therapy award”, and “het kroontje” from the Prinses Beatrix Spierfonds. She has published over 200 publications in peer reviewed international journals and books.

A very special Thank You to all of our Speakers!
Abstracts

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

- In 1932 Dr J.C Pompe described an affected 7 months old infant with massive glycogen storage in the heart and all other organs.
- In 1955 the disease was called Glycogen Storage Disease type II (GSDII).
- Between 1955 and 1969 'muscular variants' of GSDII were described with glycogen storage in the muscles but not in the heart.
- In 1963 Dr H.G. Hers discovered Acid α-glucosidase* deficiency in what he called Pompe’s disease. *the current abbreviation of acid α-glucosidase is GAA.
- In 1965 the name Acid Maltase* Deficiency was introduced.
  - acid maltase is just another name for acid α-glucosidase.
- In 1970 Dr A.G. Engel described the spectrum of AMD in terms of ‘infantile’, ‘childhood’ and ‘adult’ subtypes.
- From 1975 onwards the names GSDII, Pompe disease and AMD are used in parallel with (classic) infantile-, childhood-, (juvenile-), and adult- or late-onset subtypes.
- The abbreviations IOPD and LOPD date from after 2005 and are subject to dispute.

Part 1
- Pompe disease is about people.
- From the human body > organs > cells > compartments inside cells > lysosomes.
- From 1 single cell -the fertilized oocyte- > 37.2 trillion cells in adulthood.
- DNA as recipe.

Part 2
- From Acid α-glucosidase (GAA) deficiency > lysosomal glycogen storage.
- What is glycogen?
- From glycogen storage > muscle damage.

Part 3
- Diagnosing Pompe disease by GAA activity and DNA analysis.

Part 4
- Treating Pompe disease by Enzyme Replacement Therapy

Natural History of Infantile Pompe Disease versus New History with Treatment
Priya Kishnani, M.D.
Duke University Medical Center, North Carolina, USA
Enzyme replacement therapy (ERT) with α-glucosidase alfa for infantile Pompe disease (IPD) has improved survival. Prolonged survival has also led to a number of unanswered questions regarding the clinical course of treated disease. Long-term survivors with IPD exhibit sustained improvements in cardiac parameters, yet commonly observed findings include residual muscle weakness, hearing loss, risk for cardiac arrhythmias, hypernasal speech, dysphagia with risk for aspiration, and osteopenia. In addition, there are increasing reports of white matter (WM) involvement in the brains of children with Pompe disease. We will provide an update on the emerging phenotype in long-term IPD survivors. Continued systematic follow-up is needed to better characterize this emerging phenotype to allow for improved patient management, as well as the development of therapies to better target muscle and the CNS.

Natural History of Pompe vs New History with Treatment – Late Onset
Professor Ans T. van der Ploeg, M.D., Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands
Pompe disease presents as a clinical spectrum. This means that Pompe disease can present at any age from infancy to late adulthood. The best delineated is the classic infantile form. Patients with the classic infantile form present shortly after birth with progressive muscle weakness and a hypertrophic cardiomyopathy. Without therapy this presentation will lead to cardiac and respiratory failure and death within the first year of life. Mutations in the acid alpha-glucosidase (GAA) gene are very severe and lead to complete deficiency of GAA activity. Cells of patients with the classic infantile form may produce some acid alpha glucosidase protein, but this GAA protein is inactive. These patients are (so called) CRIM positive, Cross Reactive Immunological material positive. There are also patients with the classic infantile form that produce no acid alpha glucosidase protein at all. These patients are called CRIM negative, Cross reactive Immunological Material Negative.
All patients not presenting with the classic infantile form (non-classic or late onset) are per definition CRIM positive. This means that cells of patients produce some residual GAA activity and residual levels of GAA protein. This explains the less severe presentation. Having said this, the clinical problems experienced by children and adults with Pompe disease are as significant, but mostly they occur at a slower pace. In the vast majority of these patients the heart is spared. Cardiac hypertrophy rarely occurs in adults.

The presentation at the conference will focus on the clinical spectrum in children and adults with non-classic or late onset Pompe disease. It will highlight the presentation of symptoms in children and adults, the commonalities and the differences. Specific attention will be given to patients with the c.-32-13T>G variant and a genetic modifier which explains in part the difference in onset between adults and children with the same genotype.

Further the presentation will give an overview of the effects obtained with treatment in children and adults. What has been achieved so far and what are the current limitations that prompt us to improve treatment strategies and continue the search for next generation therapies.

**Newborn screening: Taiwan experience**
Yin-Hsiu Chien, M.D., Ph.D.
National Taiwan University Hospital, Taipei, Taiwan

Newborn screening (NBS) aims to diagnose patients with Pompe disease earlier so that timely treatment can be applied. We review and update the outcome of NBS-identified patients and discuss the limitations of the current therapy. We also address the challenges associated with caring for the babies with diagnosed acid alpha-glucosidase deficiency, but without significant clinical manifestations.

Further modifications of the current treatment and better predictive biomarkers should be explored.

**Integrative Care of Pompe Patients**
Hannerieke van den Hout, M.D., Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

More and more we learn that Pompe disease is not only a muscle but also a multisystem disease. Both classic infantile and late onset patients may have complaints of many different organs and organ-systems; i.e. the upper and lower airways, the heart, the ears and eyes, teeth, the gastro-intestinal system, the urinary system, the spine and the other bones and the joints. Patients can have intense pain, The disease does not only have a somatic, but also a psychological impact on the patient, his/her partner, children and parents. Optimal treatment of the patient asks for a multidisciplinary approach that integrates care not only over the boarders of different medical specialist but also over the boarders of age and even over the boarders of the hospital.

The presentation at the Conference will give an overview of multi-organ involvement in both Classic Infantile Pompe Disease and Late Onset Pompe Disease and will explain the importance of integrative care.

**Clinical Trial Related Issues for Pompe Disease**
Professor Benedikt Schoser, M.D., Ph.D.
Friedrich-Baur-Institute, Dep. of Neurology, Ludwig-Maximilians-University, 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 centres for neuromuscular disorders in Germany. The first Pompe patient at the FBI was diagnosed in 1974 by a muscle biopsy. Since 1974 more than 110 Pompe patients of all ages have been diagnosed; 42 within the past 10 years. We started ERT on a regular base in the year 2006. At the FBI we see 43 adults on a regular base, and 22 patients are infused every 2nd week at our institute.

My talk will be about clinical trial issues related to the Pompe patient population. Furthermore, I will talk about the scope of the European Pompe consortium (EPOC).

**Improved Muscle Function in a Phase I/II Clinical Trial of Albuterol in Pompe Disease**
Dwight Koeberl, M.D., Ph.D.
Duke University Medical Center, North Carolina, USA

This 24-week, Phase I/II, double-blind, randomized, placebo-controlled study investigated the safety and efficacy of extended-release albuterol in late-onset Pompe disease stably treated with enzyme replacement therapy at the standard dose for 4.9 (1.0-9.4) years and with no contraindications to intake of albuterol. Twelve of 13 participants completed the study. No serious adverse events were related to albuterol, and transient minor drug-related adverse events included muscle spasms and tremors. For the albuterol group, forced vital capacity in the supine position increased by 10 percent (p<0.005), and forced expiratory volume in one second increased by 8 percent (p<0.05); the six-minute walk test increased 25 meters (p<0.05; excluding one participant unable to complete muscle function testing); the Gross Motor Function Measure increased by 8 percent (p<0.005) with the greatest increases in the Standing (18 percent; p<0.05) and Walking, Running, and Jumping (11 percent; p<0.005) subtests. No significant improvements would be expected in patients with late-onset Pompe disease who were stably treated with enzyme replacement therapy. The placebo group demonstrated no significant increases in performance on any measure. These data support a potential benefit of extended-release albuterol as adjunctive therapy in carefully selected patients with late-onset Pompe disease based on ability to take albuterol on enzyme replacement therapy.
Exercise and Nutritional Considerations for the Treatment of Pompe Disease
Mark Tamopolsky, M.D., Ph.D.
Corkins/Lammert Family Neuromuscular and Neurometabolic Clinic, McMaster University, Canada

Enzyme replacement therapy (ERT) is the current standard of care for the treatment of late-onset Pompe disease (LOPD). This attenuates the decline in respiratory function and improves 6-minute walking test (6-MWT) by + 28 m over 18 months. Several studies have found that combined endurance and resistance exercise training can improve 6-MWT by as much as ERT alone and it also improves quality of life. The addition of a high protein diet and alanine to exercise training may further enhance the benefits of exercise. In theory, the addition of leucine and/or arginine could further modulate the benefits of nutrition upon muscle function. Exercise is known to modulate several of the pathophysiological features of Pompe disease including: oxidative stress, autophagic block, mitochondrial dysfunction, and muscle atrophy. Many patients are obese and this can further impair motor function (strength/mass ratio); however, weight loss is known to also lead to a loss of lean body mass and this could further impair function. Consequently, promoting body fat loss whilst maintaining muscle mass is an important goal of nutrition and exercise therapies in LOPD patients. The combination of a metabolic enhancer, optimal protein intake, exercise and ERT is likely the best long-term therapy for LOPD patients.

Respiratory Muscle Training in Late-Onset Pompe Disease: Randomized Controlled Trial Results
Harrison Jones, M.D., Ph.D.
Duke University Medical Center, North Carolina, USA

Persistent, progressive respiratory muscle weakness remains a primary obstacle to improving outcomes in patients with late-onset Pompe disease (LOPD). Respiratory muscle training (RMT) is an approach to proving resistance training to the inspiratory and expiratory muscles. We report the results of an exploratory, double-blind, sham-controlled randomized clinical trial of our 12-week RMT program in LOPD using a parallel arm pretest-posttest design. Twenty-two adults with LOPD and stable on enzyme replacement therapy were randomized to 12 weeks of RMT (n=12) or sham-RMT (n=10). The primary outcome was pretest-posttest change in maximum inspiratory pressure (MIP). Pretest-posttest change in MIP was 7.6 (standard deviation=15.9) in the treatment group and 2.7 (7.6) in the control group (P=0.4670). Similarly, pretest-posttest change in secondary outcome, maximum expiratory pressure (MEP) was 14.0 (25.9) in the treatment group and 0.0 (12.0) in controls (P=0.1854). Statistically significant differences between groups were also not identified in our other secondary outcome measures including peak cough flow, measures of physical mobility, and diaphragm thickness and thickness ratio on ultrasound. Significant between group differences were also not identified on exploratory measures from overnight sleep study (i.e., polysomnography) or patient-reported outcomes of fatigue (Fatigue Severity Scale) and sleep quality (Pittsburgh Sleep Quality Index). Patient-reported daytime sleepiness (Epworth Sleepiness Scale) was significantly improved in the treatment group relative to control (P=0.0160). Explanations for these findings include insufficient power due to greater than expected variability in response for MIP and MEP in both treatment and control groups compared to our pilot data. Additionally, despite randomization, subjects allocated to RMT were older, had been on ERT longer, and had greater respiratory muscle involvement in comparison to participants assigned to sham-RMT. Future research plans include a larger study, collaborations with other centers for the multi-site study of RMT in LOPD, and consideration of alternative study designs.

Noninvasive Respiratory Management of Pompe Disease
John Bach, M.D.,
Rutgers New Jersey Medical School, New Jersey, USA

Noninvasive Positive Pressure Ventilatory Support, not “NIV”—There are now over 1000 patients in Europe using continuous noninvasive ventilatory support (CNVS) instead of tracheotomy ventilation including numerous patients with ALS, over 500 in Canada, and over 500 in the United States and many with Pompe disease. (1) When patients need to be intubated for an acute pneumonia or for general anesthesia we extubate them back to CNVS and mechanical insufflation-exsufflation (MIE) without subjecting them to tracheotomies. This includes patients too weak to breathe at all,(2,3) Save your patients’ necks and quality of life by reading www.breatheNVS.com. Know the centers that can help you avoid respiratory complications of Pompe disease and eliminate need for trach tubes.

There is “NIV” and there is NVS. Learn the difference. Patients with neuromuscular disorders, Pompe disease, spinal cord injuries, obesity hypoventilation do not need tracheotomy tubes. Why not let them know? www.breatheNVS.com for information and contact details

References:

The IPA/Erasmus Pompe Survey: Past, Present, and Future
Nadine van der Beek, M.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

For many years, the interaction with patients and the patient organizations has been important in deepening our understanding of Pompe disease. Using patient-reported outcome measures, the IPA/Erasmus MC Pompe survey, initiated in 2002, has provided a large body of new information on children and adults with Pompe disease with regard to the disease spectrum, impact on daily living, and the effect of ERT on survival and risk for wheelchair dependency.1-5
This IPA/Erasmus MC survey, in which currently > 500 patients take part, was the ‘backbone’ for the development of the Rasch-built Pompe-specific Activity (R-PAct) scale, specifically suited to quantify the effects of Pompe disease on patient’s ability to carry out daily life activities and their social participation, which is now being used in many clinical trials investigating next-generation treatments.

Further expansion of the collaboration with the IPA, “the patients’ voice”, would provide the ideal platform for worldwide collaboration, addressing new questions arising from the Pompe community.

References (among others)

Report from Genzyme’s Pompe Registry
Virginia Kimonis, M.D.
University of California-Irvine Medical Center, USA

We report clinical data and sequence variants, in patients enrolled in the Pompe Registry, the largest database including 2,030 patients from 37 countries and 230 sites. Of these individuals 339 (16%) had Infantile Onset Pompe Disease (IOPD): with symptom onset ≤ 12 months of age with cardiomyopathy, 1510 (73%) had LOPD (Late Onset Pompe Disease) including patients with symptom onset ≤ 12 months of age without cardiomyopathy or > 12 months of age; the remainder being indeterminate. Geographically, 50% are from Europe Middle East Africa, 36% from North America and the rest from Japan and Latin America. For the IOPD group the mean age of symptom onset was 0.2 y. and age at diagnosis 0.3 y. whereas the LOPD ages there was a delay from 28.8 to 35.1 y. respectively.

Phenotypic heterogeneity is due to several factors, including different pathogenic variants in the GAA gene, which influence disease severity and manifestations. GAA sequence data from the Pompe Registry provided valuable information about the frequency and distribution of variants among patient populations. The frequency and characteristics of sequence variants, including homozygous genotypes, among patients enrolled in the Registry will be presented (Reuser AJJ 2019)

This study show how data can be successfully captured in a registry and is a means to increase understanding of the phenotypic heterogeneity seen in PD. Identification of variants is valuable for confirming diagnosis, in newborn screening, for developing treatment algorithms (e.g., immunomodulation), and improving genetic counseling.

Reference:

How Enzyme Replacement Therapy Works
Nina Raben, M.D., Ph.D.
Cell Biology and Physiology Center, National Heart, Lung, and Blood Institute, NIH, Bethesda, MD, USA

The goal of enzyme replacement therapy (ERT) is to provide normal recombinant enzymes to compensate for metabolic defects in patients with lysosomal storage diseases (LSDs). The idea of treating these diseases by administration of exogenous enzyme was first suggested by Christian de Duve in 1964. It took several decades to move from the concept of ERT to commercial development of pharmaceutical drugs for these disorders. Much of this delay can be explained by the need to understand the basic role of lysosomal enzymes in healthy cells and the mechanisms governing trafficking and receptor-mediated endocytosis of these enzymes. On top of that, the cloning and overexpression of lysosomal genes along with the generation of murine models greatly advanced the development of ERT. The therapy became a reality in the early 1990s, when its efficacy was demonstrated for the treatment of non-neuronopathic (type I) form of Gaucher disease, the most common LSD: the patients can now live essentially normal lives. This outcome stimulated efforts to develop ERT for other LSDs, including Pompe disease, a deficiency of lysosomal acid alpha-glucosidase (GAA). ERT with the recombinant human GAA made its way into the clinic in 1999 when the first clinical trials in infants began. However, the success of ERT for type I Gaucher disease has been difficult to replicate. Despite remarkable advances, the efficacy of ERT for other LSDs is somewhat limited; major issues include the inefficient delivery of the administered recombinant enzyme to the target organs, immune response, and the inability of the enzyme to cross the blood-brain barrier. In addition, the treatment is usually initiated in patients with clinical manifestations, when organ damage has already occurred.

Update on Amicus Trials with ERT Associated with Chaperone Molecule
Pascal Lafarèt, M.D., Ph.D.
Versailles Saint-Quentin-en-Yvelines University, Paris Saclay University, France.

Since the development of ERT for Pompe disease (PD), efforts were dedicated to overcoming some of the limitations of the treatment. Two main strategies, both aimed at the enhancement of the enzyme bioavailability in tissues, are now in late-stage clinical testing.

The first approach consists in the modification of the recombinant enzyme to increase the M6P residue content. The second strategy involves the use of pharmacological adjuvants to enhance ERT efficacy. Chaperones are small molecules known to
promote folding and improve stability of proteins and enzymes. In the case of PD, improved rhGAA bioavailability via enhancement of enzyme stability in blood was demonstrated in preclinical models. Different glucose analogues, acting as allosteric inhibitors of GAA, have been investigated e.g., 1-Deoxynojirimycin (1-DNJ; Duvoglustat®), 1-Deoxynojirimycin-HCl (DNJ-HCl; Duvoglustat®-HCl; AT2220) or N-buty-deoxynojirimycin (NB-DNJ, Miglustat®) and demonstrated a beneficial effect when combined with ERT.

Amicus Therapeutics developed a recombinant enzyme ([ATB200], with a higher content of M6P and bis-M6P glycan residues, which is being tested in clinical trials in association with pharmacological chaperones. Recent clinical studies sponsored by Amicus Therapeutics tested the combination of the AT2221 chaperone with the engineered enzyme ATB200 in LOPD patients (NCT02675465, AT-GAA, Amicus Therapeutics), and current available data about ongoing clinical trials will be discussed here.

**Preclinical Studies for Oral-ERT of Pompe Disease with a Tobacco Seed-Derived Recombinant Acid Maltrase**

Frank Martiniuk, Ph.D.
JME Group, Inc.

Genetic deficiency of lysosomal acid maltase or acid α-glucosidase (GAA) results in the orphan disease known as glycogen storage disease type II or acid maltase deficiency (AMD) or Pompe’s disease (PD), encompassing at least five clinical subtypes of varying severity. PD results from mutations in the GAA gene and deficient GAA activity, resulting in the accumulation of glycogen in tissues (primarily muscle) and characterized by progressive skeletal muscle weakness and respiratory insufficiency.

The current approved enzyme replacement therapy (ERT) for PD is via intravenous infusion of a recombinant human GAA (rhGAA) produced by CHO cells (Myozyme/Lumizyme, Sanofi-Genzyme) once every 2 weeks in a medical setting. Although the current ERT has proven to be very effective in rescuing cardiac abnormalities and extending the life span of infants, the response in skeletal muscle is variable. In late-onset patients, only mild improvements in motor and respiratory functions have been achieved and the current ERT is unsatisfactory in the reversal of skeletal muscle pathology. Myozyme has been a wonderful first step, but it has revealed subtle aspects that must be addressed for successful treatment. Additional challenges for ERT include insufficient targeting/uptake of enzyme into disease-relevant tissues, poor tolerability due to ERT-mediated anaphylaxis, autophagic buildup, immunologic reactions and prohibitively high cost of lifelong ERT ($250-500K/year/adult patient). Hence, novel approaches for ERT for PD are urgently needed.

Our objective is to develop an innovative and affordable approach for ERT via oral administration (Oral-ERT) to maintain a sustained, therapeutic level of enzyme on a daily basis to improve efficacy of treatment and quality of life for PD patients. To this end, we hypothesized that tobacco produced rhGAA (tobrhGAA) can be ingested daily in a capsule that allows the maintenance of a therapeutic level of enzyme. We have shown that tobrhGAA expressed in the seeds from transgenic tobacco plants is enzymatically active and can correct enzyme deficiency in GAA deficient cells and in vivo in disease-relevant tissues in GAA knockout (KO) mice-administered IP (Martiniuk et al., Applied Biochem Biotech 171:916-926,2013) and new data from our SBIR Phase I grant. Long-term daily oral treatment with whole or lyzed tobrhGAA seeds showed increased muscle strength dose dependently, tolerability, negligible antibody titers, decreased glycogen levels, increased GAA in tissues, long-term stability at room temperature, normalization of spontaneous alternation/learning, PK/BD analysis, similar enzyme kinetics as placental GAA and rhGAA and NGS-genome sequence, RNA expression and global proteomic profiling of tobrhGAA and WT plants, thereby providing support for proof-of-concept for Oral-ERT for PD. Oral-ERT is an innovative approach that overcomes some of the challenges of Myozyme and provides a more effective, safe and less expensive treatment.

**Safety and Efficacy Data Using VAL-1221 in Patients with Late Onset Pompe Disease (LOPD)**

Priya Kishnani, M.D.
Duke University Medical Center, North Carolina, USA.

Disease progression in Pompe disease, frequently associated with cytosolic accumulation of glycogen, is common despite conventional lysosomal-targeted enzyme replacement therapy. VAL-1221 is a fusion protein comprising the Fab portion of a cell-penetrating antibody utilizing the nucleoside transporter ENT-2 to gain access to the cytosol, and recombinant human acid alpha glucosidase, which promotes lysosomal uptake via mannose-6-phosphate receptors. Thus, VAL-1221 targets both cytosolic and lysosomal glycogen. In a 3-month controlled, dose-escalation study in eleven late-onset Pompe disease (LOPD) patients previously treated with Myozyme/Lumizyme at 20 mg/kg every 2 weeks for at least one year, we showed that that VAL-1221 was safe and well-tolerated and that in comparison to Myozyme/Lumizyme, it provided largely dose-dependent improvements in motor, pulmonary and patient-reported outcomes, particularly in patients with no prior history of significant infusion-associated reactions (IARs) while on Myozyme/Lumizyme. We now report on up to 15 months of treatment with VAL-1221.

**A Phase 1 Study of the Safety of AAV8-LSPhGAA (ACTUS-101) in Late-Onset Pompe Disease (LOPD)**

Dwight Koebertl, M.D., Ph.D.
Duke University Medical Center, North Carolina, USA

The development of gene therapy has advanced to a point where reversal of the effects of Pompe disease can be foreseen. Pompe disease (glycogen storage disease type II; acid maltase deficiency) is a devastating myopathy resulting from acid alpha-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. The limitations of ERT have prompted the preclinical development of gene therapy for Pompe disease that more effectively corrects GAA deficiency in muscle. Our strategy for gene therapy converts the liver to a depot for continuous secretion of GAA, accompanied by the receptor-mediated uptake of GAA in muscle. Furthermore, this liver-specific expression of GAA induces specific immune tolerance. Clinical translation of efficacious gene therapy will greatly advance treatment for Pompe disease by correcting GAA deficiency and suppressing immune responses against rhGAA.
Lentiviral Gene therapy and Antisense Oligonucleotides for Pompe Disease
Pim Pijnappel, Ph.D.
Center for Lysosomal and Metabolic Diseases, Erasmus University Medical Center, the Netherlands

Pompe disease is caused by DNA mutations in the acid alpha glucosidase (GAA) gene. The normal function of GAA is to degrade glycogen in lysosomes. GAA deficiency results in glycogen accumulation throughout the body. Classic infantile patients have progressive generalized muscle weakness, an enlarged heart, and cognitive decline. Late onset patients lack cardiac and brain pathology but have progressive muscle pathology. Enzyme replacement therapy (ERT) is available for Pompe disease, but has a heterogeneous response and high costs. Using a mouse model, we developed lentiviral gene therapy for Pompe disease. In this approach, autologous (i.e. derived from the patient) bone marrow stem cells are treated in the laboratory with lentiviruses expressing an optimized version of the GAA gene. The lentivirus permanently integrates in the bone marrow stem cells, and therefore this approach could form a life-long therapy following a single intervention. Importantly, this therapy can also reach the CNS. In mice with Pompe disease, our optimized lentiviral vector was able to fully correct pathology in the heart, skeletal muscles, and the brain. In addition, it caused long-term immune tolerance by preventing the formation of anti-GAA antibodies. We aim to prepare this therapy for clinical testing in a phase I/II trial with a focus on classic infantile patients.

The majority of late onset patients with a Caucasian background carry the variant -32-13G>T (IVS1), which causes a failed production of GAA protein. It also allows a low level of normal GAA protein production, which explains the childhood/adult onset of symptoms. We identified a potential novel therapy for these patients. This therapy is based on small molecules termed antisense oligonucleotides (AONs). These restored protein production from the IVS1 allele and GAA enzyme levels in patient-derived skeletal muscle cells. We also identified the mechanism by which these AONs restored protein production, and we developed tools for analysis, design of AONs, and in vitro model systems using human muscle stem cells. To prepare AONs for clinical implementation, we are developing methods for efficient uptake by skeletal muscle cells. We aim to further develop AONs for the treatment of childhood and adulthood onset Pompe disease.

AAV-Mediated Gene Therapy in Pompe Disease: Clinical Immunology Considerations
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Early onset neuromuscular disease (NMD) is often associated with severe or null mutations that lead to greater disease burden. The success of gene replacement strategies in this setting may be influenced by limited endogenous protein expression leading to anti-transgene immune response and loss of effective copy number in skeletal muscle due to somatic growth. In one example, Pompe disease is due to 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 defects 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 spontaneous breathing 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.

Clinical studies of AAV-mediated gene therapy have been pursued to address the fundamental aspects of gene therapy in a neuromuscular disease where patients are identified by severe early onset or newborn screening. Findings in non-clinical and clinical studies related to immune management in conjunction with AAV systemic delivery have paved the way for clinical studies in adults and younger subjects who are candidates for therapeutic AAV administration. The loss of neuromuscular junction formation is a major contributor to weakness and ventilatory failure and these deficits can be prevented by early administration of AAV-GAA. Studies which utilize next generation AAV vectors for systemic administration have led to efficient targeting of muscle and motor neurons for the early treatment of Pompe disease. Related studies in Duchenne muscular dystrophy also highlight the importance of identification and management of pre-existing anti-AAV antibodies which are able to reduce the efficacy of systemic AAV vectors. Practical considerations for the implementation of systemic AAV administration will be discussed for early onset neuromuscular disease.

Gene Therapy for Pompe Disease: From Bench to Bedside
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Pompe disease (PD) is a rare autosomal disease (OMIM #232300) due to the deficiency of the enzyme acid a-glucosidase (GAA). Mutations in this enzyme, lead to glycogen accumulation, cardiomegaly with respiratory distress, muscle weakness and feeding difficulties. Administration of the recombinant enzyme (Myozyme®, Sanofi) is the current treatment for PD. Although Myozyme® is a lifesaving treatment, variable improvement in the locomotor function were observed.

Several investigational gene therapy approaches have been developed in the past to treat PD. We developed a gene replacement therapy for PD based on adeno-associated virus (AAV) vector expressing GAA in the liver fused with an efficient signal peptide to achieve an efficient secretion of GAA in the bloodstream. Sustained, stable levels of circulating GAA corrected the disease at a systemic level. Pharmacokinetic studies comparing the efficacy of gene therapy and enzyme replacement therapy with recombinant human GAA support further development of this approach.
Skeletal Muscle Abnormalities in Pompe Disease Can Be Reversed by Enzyme Replacement Therapy

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Accumulating evidence for the role of the lysosome in health and disease has changed the way we see the pathogenesis of tissue damage in a large group of lysosomal storage disorders (LSDs). Over the course of the past decade, it became abundantly clear that the cellular pathological changes in LSDs, including Pompe disease, go far beyond the lysosome. In the case of Pompe disease, progressive intralysosomal build-up of undigested glycogen in skeletal muscle - a major affected tissue - sets in motion a whole series of “extra-lysosomal” events including defective autophagy, disruption of a variety of signal transduction pathways, cellular stress and energy deficit, and metabolic abnormalities. The currently available enzyme replacement therapy has changed the natural course of the disease and, no doubt, improved prognosis for Pompe disease patients. However, despite considerable progress, the therapy is still not satisfactory since the effect in skeletal muscle is limited. In a large pre-clinical study, a new experimental drug, AT-GAA [recombinant human acid alpha-glucosidase (GAA); Amicus Therapeutics], with much improved lysosome-targeting properties reversed or significantly improved all aspects of the disease pathogenesis. A caveat, however, is that the therapy was initiated in clinically asymptomatic GAA-deficient mice.

The Common c.-32-13T>G Splicing Variant of GAA Gene: From Functional Characterization to the Identification of New Therapeutic Targets for Pompe Disease

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The mutation profile of the GAA gene in patients affected by Pompe disease (PD) is heterogeneous; however, most patients affected by the late onset phenotype carry the splicing mutation c.-32-13T>G in at least one allele, making this mutation an interesting target for therapeutic development.

We have previously shown that this mutation affects the binding of the U2AF65 splicing factor to the polypyrimidine tract of exon 2, leading to a complete or partial exclusion of this exon from the mature GAA mRNA. However, in the presence of this mutation, variable levels of the normal spliced GAA transcript and protein are produced. Furthermore, using a series of overlapping deletion constructs we mapped several splicing silencers within the exon 2 sequence and designed different antisense morpholino oligonucleotides (AMOs) to target those regions. Using a minigene approach and patients’ fibroblasts we were able to successfully increase the inclusion of exon 2 into the mRNA and improve GAA enzyme activity (70% increase) by targeting a specific silencer with a combination of AMOs. Most importantly, treatment of patient myotubes with the AMOs combination resulted in a partial clearance of glycogen accumulation. These data suggest that in patients carrying the c.-32-13T>G mutation and retaining a substantial residual GAA activity, the AMOs effect on GAA might be enough to achieve a beneficial effect in clinical settings.

An alternative promising approach to restore normal splicing of mutated transcripts is the use of small molecules that modify splicing patterns. Therefore, we have developed a fluorescent reporter system suitable for high-throughput screening of molecules able to restore normal splicing of c.-32-13T>G mutant alleles. Using this approach, we have screened a library of 1280 FDA approved compounds (Prestwick) and identified molecules able to efficiently restore normal splicing. Among them, we have further validated the effect of deferoxamine (Defe) in fibroblasts from patients carrying the c.-32-13T>G mutation. Indeed, Defe treatment resulted in a 2-fold increase of GAA exon 2 inclusion and a significant 50% increase in GAA enzymatic activity. It is well known that Defe is an iron chelator which in turn, promotes stabilization of hypoxia-inducible factor 1 (HIF-1). Therefore, to further confirm our results and to obtain preliminary data on the possible mechanism(s) by which Defe promotes GAA exon 2 inclusion, we analyzed the effect of iron overload and the modulation of HIF-1 expression on GAA splicing and activity in fibroblasts carrying the c.-32-13T>G mutation. Our results showed that the effect of Defe on GAA splicing are mediated by changes in iron availability and are independent of Hif-1 induction. However, preliminary data suggest that besides rescuing GAA activity by promoting exon 2 inclusion, Defe would further increase the enzymatic activity by an additional mechanism independent of splicing regulation and mediated by HIF-1 induction.

In conclusion, we applied an RNA-based approach for PD drug screening and repurposing and identified new targets for the development of therapeutic molecules, which either alone or in combination with ERT could improve the clinical outcome in PD patients carrying the c.-32-13T>G mutation.

Targeting Glycogen Synthase (GYS1) with Antisense Oligonucleotide Treatment in a Mouse Model of Pompe Disease

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Background: Pompe disease is a progressive myopathy resulting from the deficiency of acid α-glucosidase (GAA). ERT with recombinant human (rh) GAA works well in alleviating the cardiomyopathy; however, many patients continue to have progressive muscle weakness from muscle glycogen accumulation produced by muscle glycogen synthase (GYS1). Previous studies have provided proof of principle that knockdown of GYS1 mRNA by phosphorodiamidate morpholino oligonucleotide conjugated with a cell penetrating peptide reduced glycogen, however was nephrotoxic. Antisense Oligonucleotides (ASO) technology has emerged as a powerful therapeutic alternative for the treatment of genetic disorders by targeting RNA. Most recently therapy for spinal muscular atrophy has been successful using ASOs and our hope is that ASO technology will be successful in Pompe disease.
Objectives: In order to impart specificity for the muscle glycogen synthase (GYS1), we used ASO-mediated gene silencing through the RNaseH1 dependent degradation mechanism.

Results: Over 150 ASOs were designed and screened in vitro to identify the most efficacious ASO for testing in wild type mice. The leads from the screen were validated in a dose response study. Three ASOs (GYS1 ASO#1, ASO#2 and later ASO#3) showed the best tolerability and efficacy profile leading to knock down of GYS1 mRNA by approximately 50% of control. We performed a pilot study of the efficacy of these three GYS1 ASOs in Pompe mice as monotherapy and reduced muscle GYS1 mRNA levels and glycogen production and autophagy markers LC3B and p62. Specifically, ASO#3 treatment increased mTOR to WT level. ASO#2 resulted in weight loss of the mice. We will present the results of the study of the effect of the GYS1 ASOs on muscle glycogen, histology, GYS1 RNA and muscle function in Pompe mice.

Conclusions: These preliminary studies provide proof of principle that GYS ASOs might be a potentially promising adjunct treatment for Pompe disease.

Stem Cell and Muscle Regeneration in Pompe
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Muscle has a large capacity to regenerate upon injury. This process is mediated by muscle stem cells. A key question is why muscle stem cells are incapable of restoring muscle in human disease. We found that in Pompe disease, muscle regeneration is compromised due to a failure in the activation of muscle stem cells. However, when provoked with an external injury, muscle stem cells in mice with Pompe disease were perfectly capable of regenerating muscle. This suggests that in Pompe disease, an activation signal is missing or that muscle regeneration is blocked. It also suggests that it is possible to restore muscle in Pompe disease by promoting the activation of muscle stem cells. We are investigating this possibility by investigating the mechanism by which muscle stem cells are regulated in Pompe disease in order to find targets for a possible therapy.

Another way to restore muscle in Pompe disease is by externally providing gene-corrected muscle stem cells that can form new, healthy muscle. To this end, we have generated stem cells (termed iPS cells) from patient-derived skin cells, and provided the correct GAA gene using the CRISPR-cas9 technology. We developed a protocol to develop muscle stem cells from iPS cells and to generate large amounts of pure muscle cells, required for transplantation. When transplanted into mouse muscle, these human muscle stem cells contributed to the generation of new, human muscle. To further optimize this approach, we have developed human mini-muscles on a chip. These consist of small muscles that grow in 3D and that can contract. The chip serves to measure the force of contraction. We are using this advanced system to investigate the conditions that are required for efficient transplantation of human muscle stem cells into human muscle with Pompe disease.
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