

2019 ISMRD Scientific Conference Summary and Report

The attendees of the 2019 ISMRD Conference on the Glycoproteinoses were welcomed to Atlanta by cooler than normal temperatures for late July but the quality of the scientific program remained “red hot”. Professionals and family participants alike spent the next three days sharing their knowledge, exchanging ideas and challenging each other to move the field ahead. Our keynote speaker, Dr. Thomas Braulke, began the session titled, “Emerging Areas in Lysosomal Biology”, with a perspective on the mannose 6-phosphate targeting pathway before sharing new findings from his group about a sorting-independent role for mannose 6-phosphate in lysosomal function. Next we heard a talk from Dr. Marco Sardiello on the function of the CLN8 protein in the sorting of lysosomal hydrolases within the early secretory pathway. His work not only has uncovered new features of lysosomal biogenesis but also pointed to new therapies that may be broadly applicable to lysosomal storage disorders. Dr. Chun-Yan Lim from UC-Berkeley shared a wonderful overview of the mTORC1 pathway and its regulation by cholesterol. His talk was followed by a presentation from Dr. Steve Walkley on the lysosomal system and its role in neurological disease. Dr. Walkley shared numerous examples where altered lysosomal function contributes to the pathogenesis of neurodegenerative disorders like Parkinson’s and Alzheimer’s, and other examples where genetic defects in diverse cellular proteins may manifest as lysosomal disease. Day One closed with a powerful and emotional talk from ISMRD Board member and advocate Daniel Peach on the challenges of living with sialidosis, and his inspiring determination to overcome the hurdles of modern medical practice and identify safe and effective treatments.

Day Two began with a session titled, “Clinical Management, Care and Support” and a talk from ML mother and real life “Wonder Woman” Sylvia Webb of Australia. Her heartfelt perspective on raising and caring for five children with ML beautifully reflected the peaks and valleys so many families face when living with the glycoproteinoses. Her talk was followed by an artfully delivered presentation from David Tonge of England about his family’s experience with alpha-mannosidosis – from the birth and diagnosis of his affected son to his treatment with bone marrow transplantation. Both Sylvia and David highlighted the resilience and strength shared by all the ISMRD families. The next two speakers in this session were Dawn Laney and Dr. Nadia Ali from Emory University School of Medicine who delivered engaging and informative talks on creating an effective medical team for patients living with rare disease, and on mechanisms for managing and relieving the stress associated with chronic conditions. This session closed with an overview of the cardiac anatomy and function and the cardiac issues that accompany the glycoproteinoses by Dr. Nick Pietrus.

Session 3 titled “Lysosomal Biogenesis and Function” commenced with a talk by Dr. Stuart Kornfeld on the GlcNAc-1-phosphotransferase enzyme and how analysis of the *GNPTAB* mutations found in ML patients lead to an understanding of the functional significance of different conserved domains within the enzyme, and how the trafficking of this enzyme within the secretory pathway is regulated. Next was an interesting presentation from Dr. Andrew Lieberman on the intersection of the lysosome with pathways involved in organelle quality control and protein homeostasis. In this talk, we were introduced to mechanisms within the cell that sense damage to lysosomes and how these damaged organelles get cleared from neurons. The next speaker in this session, Dr. Alessandra d’Azzo, provided an outstanding overview of sialidosis and galactosialidosis. Dr. d’Azzo highlighted her laboratory’s efforts to unravel the complex molecular pathogenesis of these disorders in tissues such as muscle, and how her work has pointed to new opportunities for both conventional and unconventional modes of treatment. Two short talks followed, including one from patient-scientist Jenny Klein on the application of machine learning for glycoprotein drug discovery and the role of Neu1 in neuroinflammation by Leigh Fremuth. The session closed with talks by Dr. Richard Steet and Dr. David Everman – both from the Greenwood Genetic Center - that discussed novel genetic disorders that manifest with a combination of glycosylation- and lysosomal-related phenotypes. Both disorders expand the genetic underpinnings for lysosomal dysfunction and demonstrate how disruption in different pathways within the cells can converge to impact the normal functioning of the lysosomal compartment.

Rounding out the afternoon on Day Two was the session titled, “Disease Mechanisms and Models”. The first speaker, Dr. Sandra Pohl, shared her insightful work on the bone pathology associated with MLII and MLIII, including an analysis of the different cell types involved in bone homeostasis and how the development and maintenance of osteoblasts is compromised upon loss of mannose phosphorylation. We heard next from Dr. Heather Flanagan-Steet about the role of secreted cathepsin proteases in ML pathogenesis. Her work using a zebrafish model for MLII and novel chemical probes to track cathepsin activity highlighted an emerging role for glycosaminoglycans in ML cartilage and cardiac pathogenesis. Both talks indicated new possible avenues to treat ML disease that target sensitive downstream pathways in affected tissues. This session continued with an enlightening talk by Dr. Ida Annunziata on the epigenetic control of lysosomal biogenesis and how modulation of transcription factors and histone modifying enzymes may represent novel ways to promote lysosomal and autophagic responses for the treatment of the glycoproteinoses. Her talk was followed by a presentation from Dr. Enrico Moro on MPSII and the developmental consequences of reduced IDS expression in early embryogenesis. Enrico’s findings support a role for lysosomal hydrolases in the key signaling events that drive tissue development and point to mechanisms that go beyond substrate storage as the primary drivers of pathogenesis. Dr. Charles Vite presented next and gave a

valuable overview of the large animal models that are available for lysosomal storage disorders and how they are being used to better understand and treat these conditions. This talk was followed by a presentation from Dr. Tim Wood on the development of a newborn screening platform for the glycoproteinoses and how this platform might spur early identification of and intervention for these disorders. Day Two closed with three abstract talks from Jason Weesner, Tong Wang and Beniam Berhane that reinforced the main concepts of this session and the expanding role of the lysosomal system in health and disease.

Day Three's only session focused entirely on therapy and began with a well crafted overview of gene therapy by Dr. Steven Gray from UT-Southwestern who also shared his preclinical work on the use of AAV9 for the treatment of AGU. Following Dr. Troy Lund's update on the use of hematopoietic stem cell transplantation for glycoproteinoses patients, we heard from Dr. Ritva Tikkanen on mutation-specific or "personalized" approaches to the treatment of AGU. Dr. Tikkanen's work highlighted the potential of small molecule therapies and the need to fully characterize how patient mutations affect enzyme function. Next, we heard an update from Dr. Allison Bradbury on gene therapy for mucopolidosis II, which included further characterization of the feline MLII model and evaluation of AAV9 vectors for *GNPTAB*. Dr. Arne Linhorst's presentation followed and covered the use of ERT to treat a mouse model of fucosidosis. He presented work on two alternative strategies to overcome the blood-brain barrier and achieve delivery of enzyme into the central nervous system, including the creative use of a fucosidase-lectin fusion protein.

The next two talks provided a highly valuable perspective on therapy development by two representatives from the pharmaceutical industry. Dr. Diego Ardigo from Chiesi discussed the development of ERT for alpha-mannosidosis, and the challenges associated with clinical trials. His talk was followed by a presentation from Dr. Russell Gotschall at Amicus who shared an inspiring story about the successful development of a gene therapy approach for late infantile Batten disease. Russell's talk illustrated the importance of patients, basic and clinical scientists, and industry coming together to tackle rare disease. Our session on therapy closed with two short talks by Lena Westermann and Dr. Antje Banning that covered novel therapeutic approaches for MLIII alpha/beta and AGU, respectively.

Day Three concluded with two lively roundtable discussions on the need for appropriate animal models for the glycoproteinoses, and on we can collaborate to drive therapy development. There was a productive discussion on the necessity of different research groups to organize into networks that would meet on a more regular basis to discuss next steps in research and therapy testing. In sum, this conference provided outstanding scientific talks in a wide range of lysosomal diseases and saw an unprecedented level of discussion and debate among the

professionals. There was a clear consensus that we must work together going forward to meet the future goals of ISMRD and deliver the hope of effective therapies for the glycoproteinoses.