April Research Roundtable Summary:
Glycogen as a Therapeutic Target for Lafora Disease and Adult Polyglucosan Body Disease

Chelsea's Hope hosted their first Virtual Research Roundtable on April 27th, 2023, with more than 60 attendees representing the research, clinical, and patient communities. The topic of discussion was glycogen as a therapeutic target for Lafora Disease (LD) and Adult Polyglucosan Body Disease (APBD). Our guest speakers were Dr. Kia Markussen, Dr. Pascual Sanz, and Dr. Or Kakhlon.

Dr. Kia Markussen recently completed her PhD dissertation at the University of Kentucky in Dr. Matthew Gentry's lab. Her dissertation examined metabolic signatures in multiple glycogen storage diseases. At the roundtable, Dr. Markussen discussed the distinct metabolic profile observed in the brain tissue of LD mice where many of the perturbed metabolites were directly connected to glucose and energy consumption. Excitingly, Dr. Markussen showed metabolic data from cerebral spinal fluid (CSF) in LD patients that showed the same metabolic signature found in the mouse models. This suggests that the mouse models are a good tool for understanding glycogen metabolism in LD patients.

Additionally, Dr. Markussen showed data from primary cultures of neurons and astrocytes in LD mice, revealing that they have distinct metabolic profiles. This highlights the continuing need to study specific brain regions and cell types to better understand LD progression and the potential impact of reducing glycogen accumulation in the brain. At the end of her presentation, Dr. Markussen highlighted the various therapeutic tools under development to treat LD. Of the four therapeutic tools presented, three target the enzyme glycogen synthase in order to reduce the synthesis of glycogen in the brain, thereby slowing glycogen accumulation and Lafora body aggregation. While none of those three therapeutics have yet reached clinical trials, they have been tested for efficacy *in vivo* using animal models.

Our second guest speaker was Dr. Pascual Sanz at the Instituto de Biomedicina de Valencia. Dr. Sanz was a member of the Lafora Epilepsy Cure Initiative (LECI) and continues to investigate mechanisms of LD. His areas of research include neuroinflammation, proteostasis, and pathophysiology in LD. At the roundtable, Dr. Sanz presented data from a recent publication: Deciphering the polyglucosan accumulation present in LD using an astrocytic cellular model. The Sanz lab established primary astrocytes derived from a malin-knockout mouse model, allowing them to study factors that contribute to glycogen accumulation in LD astrocytes.

In his talk, Dr. Sanz presented data that showed early polyglucosan bodies (PGBs) in astrocytes were sensitive to degradation by diastase, an enzyme that breaks starch granules into maltose units. However, mature PGBs could not be degraded by diastase. Additionally, application of AICAR, an AMP analogue, was able to reduce early stage PGB accumulation by enhancing

glycogen phosphorylase activity. This suggests that metformin is beneficial in LD patients because it increases endogenous AMP levels, increasing glycogen phosphorylase activity.

Our final guest speaker was Dr. Or Kakhlon from the Hadassah-Hebrew University Medical Center in Jerusalem. Dr. Kakhlon's research examines the development and use of small molecules to treat Adult Polyglucosan Body Disease (APBD). In APBD, patients experience loss of function in the Glycogen Branching Enzyme (GBE), which is critical for synthesizing soluble glycogen. As a result, patients with APBD develop PGBs similar to the Lafora bodies observed in LD patients. Dr. Kakhlon discussed efforts to identify small molecules that would be effective in reducing PGB accumulation in APBD mouse models and speculated on their potential efficacy for reducing Lafora body accumulation in LD models.

Thank you for reading our Roundtable Summary and please do not hesitate to contact our Science Director, Dr. Kit Donohue, if you have any questions or suggestions: katherine@chelseashope.org