April 2024 Research Roundtable Summary

Featuring guest speakers Luis Zafra-Puerta, Dr. Gentry, and Dr. Minassian

Chelsea's Hope hosted their quarterly Virtual Research Roundtable on April 11th, 2024, with more than 80 attendees representing the research, clinical, and patient communities. Our guest speakers were Luis Zafra-Puerta, Dr. Matt Gentry, and Dr. Berge Minassian.

Luis Zafra-Puerta is a researcher at the Health Research Institute of Fundación Jimenez Diaz (Dr. José Serratosa's lab). He presented his findings on the effect of Myozyme treatment in two mouse models of Lafora disease. Often, the fastest route to treatment is repurposing drugs, and Myozyme is a drug that has been approved for use in Pompe disease. Myozyme works by degrading glycogen in the lysosome, however, the data showed no effect in degrading Lafora Bodies in the mouse brain when delivered via ICV injection. This could be because it localizes to the lysosome of the cell, rather than in the cytoplasm where Lafora Bodies are located. There was also no effect observed on myoclonic jerks, memory, or anxiety in the mouse models. During the discussion, questions were asked about if it can halt accumulation of Lafora Bodies - while the effect was only studied over 31 days, there is no evidence to suggest this. It was also asked if Myozyme can degrade Lafora Bodies in the skeletal muscle - while this has not been specifically tested, this is unlikely due to the Myozyme not reaching the correct cellular location. While these data do not show the efficacy that any of us hoped for, they show how hard the research and clinical community continues to work on behalf of the patients and their families. These data will help us prioritize our efforts on the most promising therapeutic strategies going forward.

Dr. Matt Gentry is the Director of the Lafora Epilepsy Cure Initiative (LECI) and Chair of Biochemistry & Molecular Biology at the University of Florida. He presented an update on VAL-1221 treatment in Lafora disease. VAL-1221 is a fusion protein, combining the enzyme (recombinant human acid alfa glucosidase: i.e. Lumizyme/Myozyme) with a nucleoside transporter in order for it to gain access to the cytoplasm of the cell where it can target Lafora Bodies. Dr. Gentry showed that VAL-1221 achieves good bio-distribution in mouse and canine models when ICV injection is used. Data reveal that after 7 days of administration, the Lafora Bodies were significantly cleared and the metabolic profile matched the wildtype animals. During the discussion, a question was asked about the efficacy of IV administration rather than ICV, since the compassionate use protocol requires IV administration. However, because VAL-1221 does not cross the blood-brain barrier, data suggest that ICV administration would be required in order to clear Lafora Bodies in the brain. It can be a long path (possibly several years) to find collaborators in industry to test and approve a new drug delivery system. Despite this challenge, it is encouraging to see the positive impact of this drug in the animal models.

Dr. Berge Minassian is the Chief of Child Neurology at UT Southwestern Medical Center. He has been active in neurogenetics throughout his entire career and is a dedicated clinician treating Lafora disease patients. He announced that on April 11th, his team submitted an Investigational

New Drug application to the FDA for a safety study of ION283 ASO therapy. In 30 days, we will have one of three responses from the FDA: they could deny permission for the study, ask for some revisions, or allow the study to launch. The full set of inclusion/exclusion criteria for participation in the study was not discussed, but a general guideline was that patients still able to walk on their own are likely to be eligible for the study. Patients currently on other experimental therapies would also be eligible for the study; however, there would be a required wash-out period - they cannot be on both ION283 and other experimental treatments at the same time. Dependent on funding, the goal is to enroll ten patients initially, who will need to be referred by their physicians. The estimated cost is 1.5 million for a 2-year study (while Ionis is providing the drug free of charge, the funding raised will cover clinical costs associated with the study). The safety study will be held at UT Southwestern Medical Center in Dallas, Texas, and participants would have to be present in Dallas for treatment and assessment for about five days every three months. Participants would be responsible for covering travel costs, including travelers' health insurance and accommodation; however, Chelsea's Hope will work to locate resources for families who need financial support to cover travel costs. UT Southwestern has a lot of experience with international patients and has previously partnered with Ronald McDonald House, which provides accommodation and meals for patients and their families. Following FDA review, the information about the safety study will be found on clinicaltrials.gov, and will have the inclusion/exclusion criteria, protocol, and contact information. People will be able to donate to a foundation at UTSW to support running the study. Donations to the fund will have no impact on who is selected to participate in the trial! Chelsea's Hope will send out details when the site for receiving funds is launched. This is a hopeful step forward in our continued efforts to secure treatment for patients with Lafora disease.

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

Summarized by Maysoon Hussain, Chelsea's Hope Science Communications Intern.
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