Kennedy Krieger
Moser Center for Leukodystrophies

2024 End-of-Year Report

Greetings, LBSL family and friends of Kennedy Krieger:

As we begin the new year, we would like to take this time to reflect on the past year's advances in the field of LBSL, and share updates on our ongoing and new partnerships.

This past July, we held our biennial **LBSL Patient and Scientific Conference**, and it was our biggest yet. We had over 150 registrants in total, from eight countries, and we were happy to host more than 60 people in person each day. Highlights of the three-day event included a wonderful welcome reception at the hotel, complete with an activities room for our kids and teens organized by Cure LBSL's director of patient engagement, **Melody Kisor**. Here's a rundown of what we were able to accomplish over those days:

Day 1 of the conference focused on the natural history of LBSL, on clinical care and trial readiness, and on representing the patient voice:

- **Amena Smith Fine, MD, PhD**, gave updates on LBSL clinical research, including progress on developing outcome measures for trials using wearable accelerometers at Kennedy Krieger Institute, Amsterdam University Medical Center and the University of Helsinki.

- A team from the National Institute of Health's Metabolism, Infection and Immunity (MINI) study, including **Eliza Gordon-Lipkin, MD**, discussed guidelines for managing infection and fever in LBSL and how these factors may influence disease status, based on the team's experience with other mitochondrial disorders.

- Representatives from the Food and Drug Administration (FDA) (**Michelle Campbell, PhD**) and Combined Brain (**Zollie Yavarow, PhD**) shared insight on gene therapy and trial readiness from the patient and family perspective.

- The afternoon began with the panel "Caring for Medically Complex individuals," moderated by a Moser Center team that included neurologist **Maura Ruzhnikov, MD**; physiatrist **Nancy Yeh, MD**; palliative care specialist

Melanie Brown, MD; and social worker **Sydney Faw, LMSW**, with patient and parent participation.

- The next panel, "Sleep, Energy and Rest for Patients With Mitochondrial Disorders," was moderated by **Jennifer Accardo, MD**, from the Children's Hospital of Richmond; **Alex Sercel, PhD**, director of scientific affairs at MitoWorld; and patient **Ed Blakey, Esq.**

- Ed Blakey also contributed to the discussion on physical therapy and rehabilitation with Moser Center physical therapist **Jennifer Keller, MS, PT**.

- The day ended with a Scientific Social, allowing scientists and clinicians to network and develop relationships that could lead to a better understanding of LBSL patient care and *DARS2* functioning.

Day 2 of the conference focused on the science of LBSL and included talks by Kennedy Krieger researchers, who shared our latest data on gene therapies for the disorder:

- **Christina Nemeth Mertz, PhD**, reviewed the use of antisense oligonucleotides (short synthetic strings of RNA—similar to the COVID-19 vaccine, for example) to mask the most common variant associated with LBSL. The data is promising: This approach appears to allow patient cells to produce more *DARS2*—and therefore function better—while in a Petri dish.

- **Ines Garofolo, BS**, and **Bayley Lindsay, BS**, summarized their work testing AAV9 (a nonpathogenic virus that delivers the full-length, healthy *DARS2* gene)—both in mice and in patient cells.
    - They found that for both mice and for patient cells, delivery of full-length *DARS2* improves functioning and survivability.
    - These data continue to serve as proof-of-concept material for our continued conversations with the National Institutes of Health, the FDA and potential funders. We recently submitted these data for publication in Annals of Neurology, and once they've been accepted, they will be available for all to read.

- **Georg Oeltzchner, PhD**, from Johns Hopkins Medicine, and **Johan Van Hove, MD, PhD**, from the University of Colorado, discussed the basics of biomarkers and the complexity and process of validating biomarkers for disorders such as LBSL.

- **Kathryn Morelli, PhD**, from the University of Vermont, and **Haissi Cui, PhD**, from the University of Toronto, both biochemists with an interest in tRNA

synthetases, reviewed their current work studying RNA therapies and synthetase function and dysfunction in disease.

- **Marni Falk, MD**, of Children's Hospital of Philadelphia, and **Marc Engelen, MD, PhD**, from Amsterdam University, both shared exciting data on novel models to study LBSL. Dr. Falk's extensive work with *c. elegans* and Dr. Engelen's novel humanized mouse model, once ready, will serve as excellent test beds for future study.

Our team at Kennedy Krieger continues to be interested in better understanding the prevalence of LBSL and how to identify and diagnose patients more efficiently. With the help of Cure LBSL, we have partnered with the **Broad Institute**'s variant curator team, which has spent the last year closely examining *DARS2* variants in the population and how to use them as predictors of prevalence. The data gathered through the partnership will help us better understand patient data, which we can leverage to develop better treatment strategies.

The conference serves as a benchmark for our community, updating everyone on our work and tracking our progress on the roadmap to a cure. The therapies we have developed show that gene replacement is sufficient to change the trajectory of disease, and now we are working toward producing a vector that can be used in humans. This step is important, as this human-ready product will need to be tested again for functionality and safety in different species. Safety in different species may suggest a similar profile of safety in humans and is a required piece of the puzzle for the FDA.

Looking ahead, we are excited to announce our participation in—and support for—Cure LBSL's **patient-focused drug development (PFDD) meeting with the FDA** in August of 2025. This is a critical step forward in defining clinically meaningful outcome measures and positioning the community for trial readiness.