Kennedy Krieger

Moser Center for Leukodystrophies

April 2026

To the Leukodystrophy Community:

We hope this letter finds everyone well and in the company of loved ones.

At the Moser Center for Leukodystrophies at Kennedy Krieger Institute, we have much to be thankful for, including our hardworking team and the trust and support of this inspiring network of patients, caregivers and families.

First, we would like to introduce you to the newest Moser Center staff members, who joined us in 2025:

Sonum Bharill, MD, MHS

Dr. Sonum Bharill is a pediatric endocrinologist at the Moser Center and an Assistant Professor of Pediatrics at the Johns Hopkins University School of Medicine. Her main interest is in adrenal disease and steroid metabolism in children. She recently joined our Leukodystrophy Clinic to provide endocrine services to children with adrenoleukodystrophy and other leukodystrophies. She often teams up with our other providers to see patients in our Leukodystrophy Newborn Screening Follow-Up Clinic.

Antonio Holmes, BA

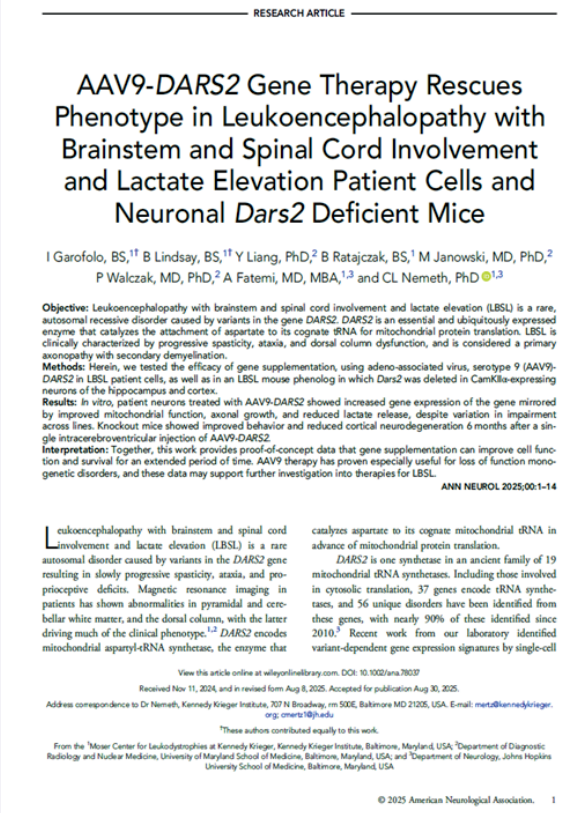
Antonio Holmes joined the Basic Science Research Lab as a Research Assistant and oversees all of our animal model work. He is a recent graduate of the University of Maryland, Baltimore County, and has excelled in all aspects of animal husbandry.

Madison Yorkowski, BA

Madison Yorkowski joined the Moser Center last summer and is also from the University of Maryland, Baltimore County. She is a Research Assistant and has taken to the field quickly, growing and maintaining neuronal and organoid cell cultures for various ALD projects.

GENERAL UPDATES FROM THE MOSER CENTER

Our team members at the Moser Center have been busy with many research activities for various diseases. Despite the tough funding environment, we have been successful in securing several foundation and federal grants. Notably, the Moser Center serves as one of the three lead sites of the Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN), which is one of the 21 Rare Disease Clinical Research Networks (RDCRN) funded by the National Institutes of Health (NIH). Last fall, we received a notice of funding renewal for this consortium to continue for five more years. The goal of this network is to conduct the largest natural history study of all leukodystrophies across several expert sites in the U.S., with the aim of developing the clinically meaningful outcome measures necessary for clinical trials. In addition to allowing us to conduct a study on all leukodystrophies, this grant also provides funding for a biomarker study for leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), which will be conducted at Kennedy Krieger in collaboration with Stanford University and Johns Hopkins. We have secured several other grants for research on various diseases—see details below. In total, our investigators published 15 journal articles in 2025 related to leukodystrophies.



RESEARCH ARTICLE

AAV9-*DARS2* Gene Therapy Rescues Phenotype in Leukoencephalopathy with Brainstem and Spinal Cord Involvement and Lactate Elevation Patient Cells and Neuronal *Dars2* Deficient Mice

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Objective: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare, autosomal recessive disorder caused by variants in the gene *DARS2*. *DARS2* is an essential and ubiquitously expressed enzyme that catalyzes the attachment of aspartate to its cognate tRNA for mitochondrial protein translation. LBSL is clinically characterized by progressive spasticity, ataxia, and dorsal column dysfunction, and is considered a primary axonopathy with secondary demyelination.
Methods: Herein, we tested the efficacy of gene supplementation, using adeno-associated virus, serotype 9 (AAV9)-*DARS2* in LBSL patient cells, as well as in an LBSL mouse phenolog in which *Dars2* was deleted in CamKIIa-expressing neurons of the hippocampus and cortex.
Results: In vitro, patient neurons treated with AAV9-*DARS2* showed increased gene expression of the gene mirrored by improved mitochondrial function, axonal growth, and reduced lactate release, despite variation in impairment across lines. Knockout mice showed improved behavior and reduced cortical neurodegeneration 6 months after a single intracerebroventricular injection of AAV9-*DARS2*.
Interpretation: Together, this work provides proof-of-concept data that gene supplementation can improve cell function and survival for an extended period of time. AAV9 therapy has proven especially useful for loss of function monogenetic disorders, and these data may support further investigation into therapies for LBSL.

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Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a rare autosomal disorder caused by variants in the *DARS2* gene resulting in slowly progressive spasticity, ataxia, and proprioceptive deficits. Magnetic resonance imaging in patients has shown abnormalities in pyramidal and cerebellar white matter, and the dorsal column, with the latter driving much of the clinical phenotype.[1,2] *DARS2* encodes mitochondrial aspartyl-tRNA synthetase, the enzyme that catalyzes aspartate to its cognate mitochondrial tRNA in advance of mitochondrial protein translation.

DARS2 is one synthetase in an ancient family of 19 mitochondrial tRNA synthetases. Including those involved in cytosolic translation, 37 genes encode tRNA synthetases, and 56 unique disorders have been identified from these genes, with nearly 90% of these identified since 2010.[3] Recent work from our laboratory identified variant-dependent gene expression signatures by single-cell

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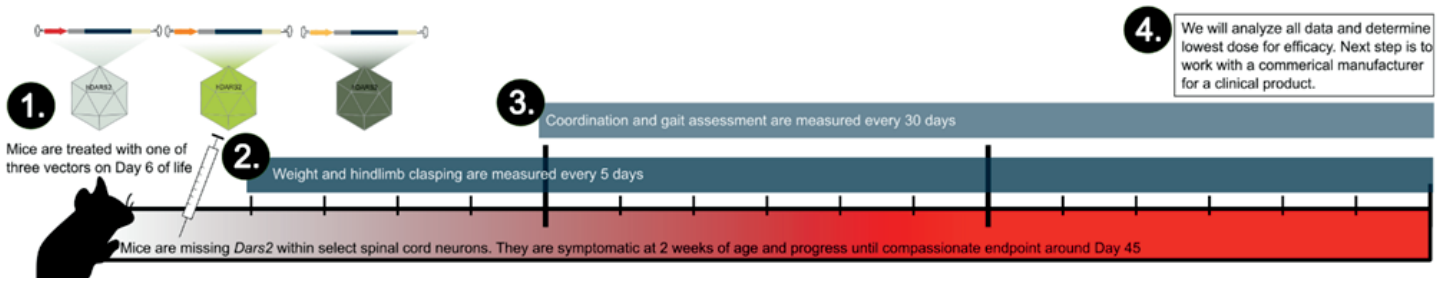
We continue to serve as strong advocates for individuals affected by leukodystrophies. One great accomplishment in 2025 was to have metachromatic leukodystrophy (MLD) added to the Recommended Uniform Screening Panel (RUSP). This was the result of hard work by many scientists and advocates, and we were fortunate enough to have our own Eric Mallack, MD, MBE, an expert in leukodystrophies, provide a congressional briefing at the U.S. Capitol to emphasize the need for MLD newborn screening.

PROGRESS IN LBSL

It has been a busy year in the research lab, with tireless efforts to advance our AAV9 therapeutic to clinic. We reached a milestone in this project last year, as we published our findings in a prestigious peer-reviewed research journal, Annals of Neurology. This work demonstrates that our research vector successfully prevents the onset of an LBSL-like phenotype in mice that lack the LBSL-causing gene, Dars2, in parts of their brain. This vector also successfully improves viability and function of neurons that were grown from LBSL patient cells. This work would not be possible without your blood donations or your financial support, and for that, we are very grateful.

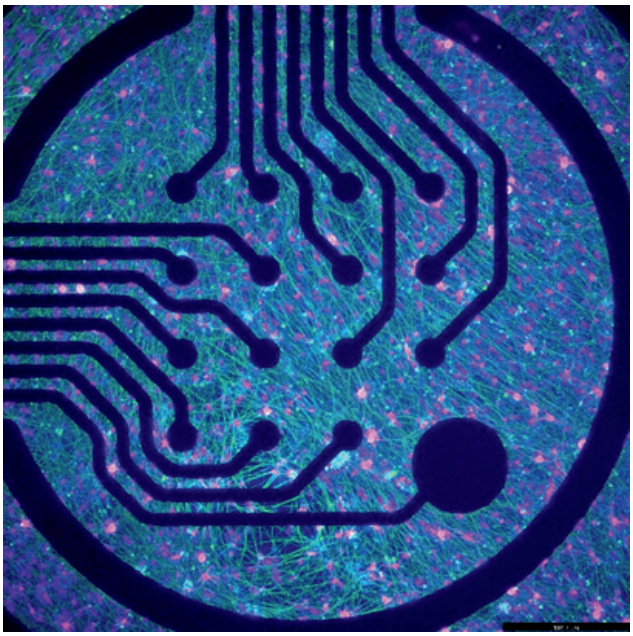


Experimental plan: Three vectors, differing from each other only in their promoters, are currently being tested in mice. The mice are assessed frequently for general health and phenotype. The most effective vector at the lowest dose will be recommended for clinical production.

Testing proof-of-concept ideas, such as AAV9 use in treating LBSL, requires a research-grade vector that ensures expression but is also trackable. This type of vector allows us to observe not only **where** in the brain and body it goes, but also **what** types of cells the vector reaches. Following this initial proof-of-concept work, the vector requires optimization to ensure it is safe for use in humans. This requires removing elements that make the vector trackable (e.g., a protein that makes cells turn green for easy identification), and insertion of promotors (sequences that turn expression on) that have previously been proven safe for humans in Clinical Trials. We were fortunate to have these clinical vectors designed and produced for free by generous collaborators and field experts. We have these novel vectors in hand (we have three, to help ensure the success of at least one), and we are testing them in mice to reconfirm efficacy before proceeding to clinical production. See the experimental plan above.

Much of our last year has been spent finding collaborators, confirming clinical vector design, producing the vectors and now testing them. Although our focus is on developing a successful gene therapy for LBSL, we continue work in the lab to better understand LBSL and how variants in DARS2 lead to varying presentations of the disease. We are grateful to our LBSL community and patients who have donated their blood over the years to help us generate induced pluripotent stem cells (iPSCs). We then turn these iPSCs into neurons, which become our best asset for understanding how LBSL affects the central nervous system. We can do amazing things with these cells, including measuring their “firing”—or electrical—activity using microeletrode arrays.

Madison Yorkowski does just this, and then uses antibodies to “stain” the cells, making different parts of the neurons visible under a microscope. Science can be beautiful!



Neurons grown over electrodes: Patient neurons are measured for their electrical activity over time, “stained,” and imaged under a microscope.

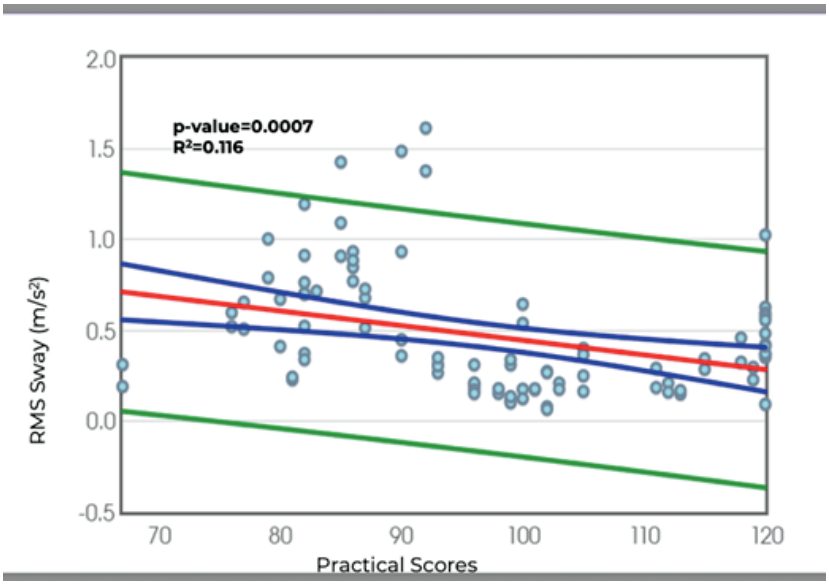
CLINICAL RESEARCH UPDATES

Last year, we focused on continuing virtual visits as part of the LBSL natural history study. We presented findings from the natural history study at the United Leukodystrophy Foundation, Child Neurology Society and American Society of Human Genetics conferences.

We found that balance impairment in LBSL is associated with poor daily adaptive functioning, especially for daily tasks people perform at home. **This finding is important because it shows that the sway data we collect using wearable sensors during virtual visits is directly linked to quality of life for individuals with LBSL.** This clinically meaningful measure can now be used as a critical metric for measuring improvement when we conduct clinical trials.

General Adaptive Composite (GAC) Practical Scores vs. RMS Sway

LBSL participants report low practical adaptive functioning relative to peers in the general population. LBSL patients reporting lower daily adaptive functioning show worse sway on standing tests with feet apart and eyes closed.



We also presented data showing that a progressive balance exercise training program, performed remotely, improved body sway and ataxia scores in a teenager with LBSL. Finally, we made progress in trying to understand connections between DARS2 variants and clinical prognosis in LBSL, showing for the first time that certain variant types are associated with worse motor and cognitive functioning.

We've also been busy preparing for the newly funded GLIA-CTN project that will investigate brain lactate as a monitoring and prognostic biomarker in LBSL. This study will involve obtaining magnetic resonance spectroscopy (MRS) imaging of brain lactate, along with obtaining measures of walking, balance and quality of life for individuals with LBSL over a two-year period. Study sites include both Kennedy Krieger and Stanford University. We look forward to placing a call for enrollment soon—study announcements will be coordinated with the Cure LBSL team.

Our research group was also happy to support Cure LBSL as they hosted an externally-led Patient-Focused Drug Development (EL-PFDD) meeting with the FDA in August 2025. Dr. Amena Smith Fine provided the clinical overview of LBSL for the meeting. She is currently working with Cure LBSL to write the "Voice of the Patient" report, which summarizes the meeting, and to prepare it for peer-reviewed publication. The PFDD publication will be another critical document for providing guidance to regulatory agencies on optimal clinical trial design.

CLINICAL TRIALS IN LEUKODYSTROPHIES

As we work toward developing the best therapeutics for LBSL and designing clinical trials for this disease, our center is heavily involved in conducting trials in other leukodystrophies. This will provide us with ample experience for the clinical trials stage of developing therapeutics for LBSL. For example, we are currently conducting a placebo-controlled trial of leriglitazone for adults with cerebral ALD, and we are actively recruiting patients for this study. Additionally, we have an expanded-access program for the use of leriglitazone for men with AMN who were previously in a placebo-controlled trial. And in collaboration with the Johns Hopkins Bone Marrow Transplant Team, we treat patients with ALD and CSF1R-related leukodystrophy with stem cell transplantation.

Lastly, several trials for other leukodystrophies are in a contracting stage. These trials include a collaboration with the industry to conduct N-of-1 trials of antisense oligonucleotides. We are fortunate to have received support from the Dresher Foundation to fund this N-of-1 program.

IN CLOSING

We can only hope that 2026 brings peace and joy to all of you. We will continue to be here, working to understand and better treat LBSL. We are grateful for you, the community, for your optimism and trust. Should you be interested, we always welcome participation in research, in any form, or other community engagement. We look forward to seeing you all in 2026, wherever that may be.

Sincerely,

Ali Fatemi, MD, MBA

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