Kennedy Krieger
Moser Center for Leukodystrophies

January 2025

To the Leukodystrophy Community:

We are excited to provide you with a 2024 end-of-year research update from the Moser Center for Leukodystrophies. Last year, our center celebrated the 100th birthday of the late Dr. Hugo Moser, and we will continue to celebrate Dr. Moser throughout 2025.

The Legacy of Dr. Hugo Moser

Hugo Wolfgang Moser was born in 1924 in Bern, Switzerland, the son of an Austrian actress, Maria, and German art dealer, Hugo. He spent his early years in Berlin. In 1933, his family was forced to flee Nazi Germany. Over the next seven years, they moved first to Switzerland, then to the Netherlands, the Vatican, and later to Cuba on their journey to safety. In 1940, they emigrated to the U.S.

The young Hugo spent his first few years in the U.S. in Baltimore, western Massachusetts and New York City. He was accepted into Harvard College in 1942, but then left in 1943 to serve in the U.S. military. Upon his return, he enrolled in Columbia University's medical school and earned his medical doctorate in 1948. Following an internship at Columbia, he went to Harvard Medical School, where, in the 1950s, he received training in medicine and neurology. During those years, he was also deployed as an army medical officer in Korea and obtained a master's degree in biochemistry at Harvard.

After completing his residency at Massachusetts General Hospital, he joined the Harvard faculty and eventually became a full professor in neurology, and the research director and later superintendent of the Fernald State School. There, he founded the Eunice Kennedy Shriver Center, one of the first research facilities for studying intellectual disability and the developing brain.

During these formative years, he made many seminal discoveries, including the discovery of the biochemical basis of multiple sulfatase deficiency and Farber's disease. It was also during these years that Hugo met the young laboratory technician Ann Boody, which led to a long and exceptional professional and marital partnership that lasted until Hugo's passing in 2007.

In 1976, Dr. Moser was recruited to serve as the president of the John F. Kennedy Institute, later renamed Kennedy Krieger Institute. During his tenure at Kennedy Krieger, Dr. Moser dedicated his work to adrenoleukodystrophy (ALD). He, Ann and other collaborators worked together to develop the very long-chain fatty acid (VLCFA) test for ALD and other peroxisomal disorders. They also developed the first dietary therapies for ALD and oversaw the first bone marrow transplantation for ALD. Later on, the Mosers and their collaborators developed the first newborn screening assay for ALD, which in 2015 led to the establishment of nationwide newborn screening for ALD.

Dr. Moser had a dramatic impact on the field of leukodystrophies and neurogenetics, not just through his own accomplishments but through his empathetic, collaborative approach, through which he inspired hundreds of other medical professionals to pursue excellence in medical research, particularly in leukodystrophies. Many of his mentees have gone on to become leaders in neurology and leukodystrophy. His humble, caring character and tireless commitment to individuals with rare diseases have left a lasting legacy with us. In celebrating his 100th birthday, we aspire to do the very best we can to fill his shoes.

With that, and as we once again find ourselves at the start of another year, we want to take some time to reflect on our work at the Moser Center for Leukodystrophies and within the ALD community.

The Moser Center's research program aims to translate new discoveries from bench to bedside. Our laboratory research team includes experts in molecular biology, stem cell research and wet lab animal research, while our clinical research team studies patients with leukodystrophies and brings new therapies to the bedside.

New Staff Members at the Moser Center

Nadav Weinstock, MD, PhD, a resident physician in pediatrics and medical genetics at Johns Hopkins Medicine, joined our research lab in early 2024. Dr. Weinstock brings with him a wealth of knowledge from his graduate work with Dr. Laura Feltri, a pioneer in the field of myelin biology. Dr. Weinstock has been balancing his time between the lab, clinic work and his family, but has within a short time made a great impact on our research. He brings with him new techniques and creative ideas, along with the passion and motivation to follow through on them. His interests lie within peroxisomal biology and myelin composition and maintenance, and how these factors come together to precipitate ALD. These interests and passions have already resulted in a 2024 Emerging Investigators Award from ALD Connect. We are very grateful to have Dr. Weinstock in the lab.

Yousif Almehza, MS, a recent graduate of The Johns Hopkins University's master's program in biotechnology, did his undergraduate work at the University of Warwick in the U.K. He joined the Moser Center's research team last October and has previous research experience studying ocular phenotypes in genetic disorders. Within our group, he works with induced pluripotent stem cells and organoids, or mini-brains, that are derived from the blood of patients with ALD.

Aditii Makwana, MS, holds a bachelor's degree in life sciences with a specialization in neuroscience and a master's degree in neuroscience from Queen's University in Canada. During her undergraduate years, she studied the association of early onset psychiatric disorders with rapid eye movement sleep behavior disorder, and the incidence of acute onset restless leg syndrome in stroke patients. She joined the Moser Center as a research coordinator in January 2024, and she serves as lead coordinator for all leukodystrophy natural history studies. Through these studies, she manages the collection of medical records, biological samples, MRIs and wearable accelerometry measures.

Brianna Reed, MS, holds a Bachelor of Science in biology and a Master of Science in biotechnology. She joined the Moser Center in July 2024 and is interested in neurology and advocacy for neurological and rare diseases. Her goals are to raise awareness in underserved communities, support patients and caregivers, and research innovative approaches to treatment and care. With over two years of experience in clinical research and trial coordination, she is our primary coordinator for clinical trials for ALD treatments.

Victoria Krechting, MS, joined the Moser Center in July 2024. She holds a Bachelor of Science in biology from Fordham University and a master's degree in bioethics from The Johns Hopkins University. Her master's thesis focused on the ethical implications of doing genetic testing in children. In addition to studying startup operations, she is managing regulatory submissions for the team's trials and projects.

Basic Research Updates

Our laboratory is primarily focused on understanding disease mechanisms and developing new therapeutics for ALD and leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL).

Studying Brain Lipid Metabolism in ALD

Dr. Nadav Weinstock has been working on a project to better understand the inflammatory and metabolic consequences of ALD macrophages that digest the brain's white matter, also called myelin. A common finding in leukodystrophy is the loss or breakdown of myelin, which leads to myelin digestion, by native inflammatory cells. This project explores the idea that ALD inflammatory cells are incapable of efficiently metabolizing ALD myelin, and that this inefficient metabolization leads to neuroinflammation and the progression of ALD.

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While these experiments are ongoing, we have found exciting preliminary results suggesting that myelin from people with ALD is more toxic to macrophages than myelin from mice with ALD. In collaboration with **Ann Moser**, we are analyzing and comparing the lipid composition of purified myelin from mice with ALD and from patients with childhood cerebral ALD. Preliminary results suggest that human myelin is, indeed, significantly different from mouse myelin, potentially explaining the limited phenotype of the mouse model of ALD. Furthermore, these results may provide us with a window into better understanding some long unanswered questions related to ALD pathogenesis.

Gene Editing in ALD

A new project in 2024 stemmed from a collaboration between the Moser Center and **Greg Newby, PhD**, a molecular biologist from the Department of Genetic Medicine at the Johns Hopkins University School of Medicine. This work, led by the Moser Center's **Christina Nemeth Mertz, PhD**, employs base editing, or changing single nucleotides of a DNA sequence, to increase the expression of genes that may be able to compensate for the loss of function of the gene *ABCD1* in ALD.

The sequence and functioning of the gene *ABCD1* are very similar to that of *ABCD2*. Since the late 1990s, researchers have been looking at ways to increase activity of *ABCD2* to compensate for the loss of functioning of *ABCD1*. While this concept has been proven to work, the drugs that can do this are indirect and lead to significant side effects.

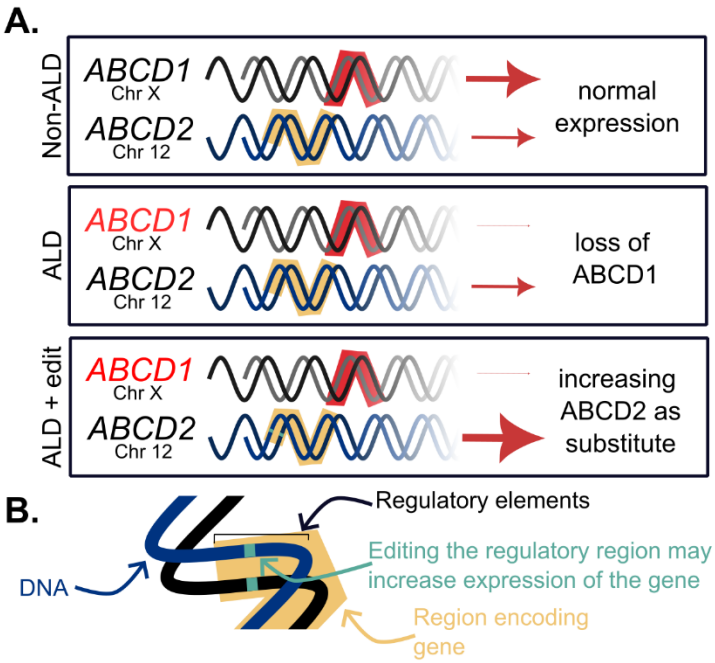

Figure 1. (A). *ABCD1* and *ABCD2* have roughly 70% homology. Under healthy conditions, *ABCD1* processes most VLCFAs. In ALD, *ABCD1* is not functional, leading to an accumulation of VCLFAs. We and others hope that by increasing activity of *ABCD2*, we can reduce VLCFA accumulation. (B). By making small changes to the DNA sequence early on in our gene of interest, *ABCD2*, we can alter (here, increase) the expression of that gene.

Other studies supporting this concept have used transgenic models, which are not feasible in humans. But with CRISPR and other gene-editing technologies that manipulate endogenous processes, we are now able to "edit" DNA to affect gene functioning. Since many different *ABCD1* variants are associated with ALD, we are targeting *ABCD2*.

Using technology that Dr. Newby helped pioneer, we are modifying *ABCD2*'s regulatory elements (regions that affect gene regulation) in the early parts of the gene. By making these small modifications, we can increase the amount of gene product, or protein, that this gene produces. We hope this will help break down accumulated VLCFAs and reduce the consequences of their buildup.

This is exciting work, as it offers a novel and direct approach to reducing VLCFA accumulation and is independent of a patient's specific *ABCD1* variant. Dr. Nemeth Mertz presented the preliminary results of this work at the 2024 annual ALD Connect meeting in Washington, D.C.

Clinical and Translational Research Updates

Bringing Novel Therapies to the Bedside

Dr. Eric Mallack and our clinical trials research team have launched and enrolled patients in a new interventional clinical trial aimed at slowing disease progression in patients with adult cerebral ALD (CALYX, NCT05819866). Dr. Mallack holds a new investigator-initiated Investigational New Drug (IND) for using leriglitazone to treat men with adrenomyeloneuropathy (AMN) who were previously enrolled in the ADVANCE study. We also recently completed a multicenter Phase I study of the thyroid mimetic VK0214 in adult men with ALD. In 2025, we will expand our clinical trial efforts to other leukodystrophies, including metachomatic leukodystrphy, Pelizaeus-Merzbacher disease and vanishing white matter disease. Our clinical research team is also developing an N-of-1/N-of-few precision therapeutics program in partnership with Johns Hopkins.

Imaging the Disease Burden in Patients

Dr. Mallack has started a new collaborative research project with Johns Hopkins and Kennedy Krieger's F.M. Kirby Research Center for Functional Brain Imaging, along with his previous team at Weill Cornell Medicine, to investigate myelination and neurodegeneration in adult and pediatric cerebral ALD using novel MRI sequences. This work aims to investigate potential novel mechanisms in the development of cerebral ALD.

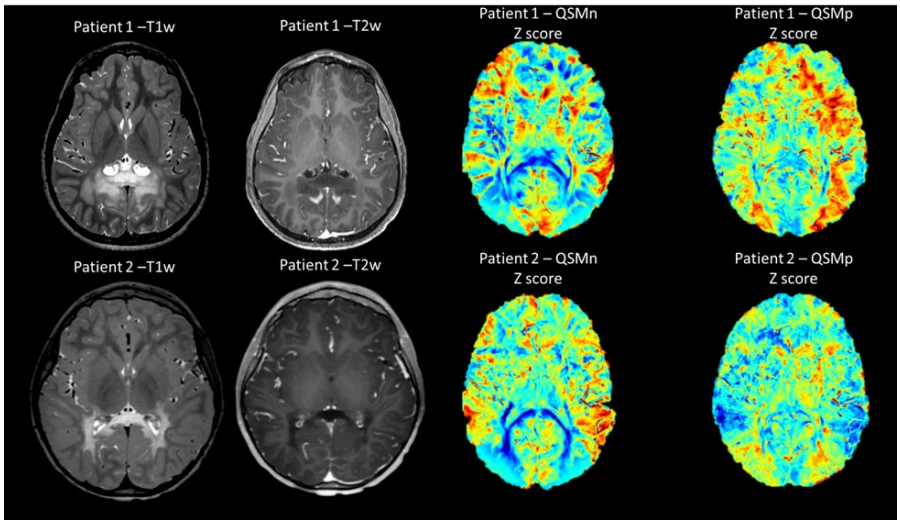

Figure 2. Example cases of two patients with cerebral ALD. In this atlas, which we derived from age-matched controls, the first two columns present structural T2w and T1w post-contrast images, while the second two columns demonstrate the Z-scores of the negative and positive quantitative susceptibility maps for each patient with cerebral ALD. These preliminary findings indicate pathological alterations in myelin and potentially iron, not only within the cerebral lesion, but also in areas of the brain that appear normal.

Identifying New Biomarkers in AMN Using Machine Learning

The National Institutes of Health recently awarded us, along with three other awardees, a multicenter grant to identify new biomarkers for AMN. Collaborating with us will be Johns Hopkins colleagues, Dr. Jaspreet Singh's group at Henry Ford Health in Detroit, and the leukodystrophy teams at Massachusetts General Hospital and Children's Hospital of Philadelphia.

The proposed longitudinal study is significant because it is expected to result in the development of an AI tool for predicting which patients are likely to worsen clinically over time. It is also expected to provide outcome markers for clinical practice and clinical trials in AMN. Importantly, it will allow us to move from the population-level comparisons of cross-sectional studies to a precision-medicine approach, establishing markers to represent and predict the disease progression trajectory in each affected individual.

This study is the first step in a continuum of research expected to lead to the development of readily accessible plasma micro-RNA (miRNA) and metabolite biomarkers, both of which can be used to indicate disease severity. *ABCD1* gene defects cannot predict the future phenotype course of the disease, and there are no plasma biomarkers identified for AMN to date. Over the course of the study, we expect to identify plasma biomarkers and biomarker signatures for monitoring and predicting disease progression in men and women with AMN, and to use these biomarkers and signatures to create and validate a machine learning-based prognosis prediction tool.

Identifying Novel Leukodystrophy Genes

The Moser Center's genetic counselor, **Julie Cohen, ScM, CGC**, helped establish the Leukodystrophy Genomic Curation Expert Panel (also known as the LeukoGCEP). Knowledge of the genetic basis of leukodystrophies is expanding at a rapid pace. There are more than 240 known genes affecting myelin, and several new leukodystrophy-associated genes are discovered each year. The purpose of the LeukoGCEP is to curate and evaluate the evidence base for a particular gene's role in causing a leukodystrophy or related disorder. This process is essential to defining the clinical relevance of genes and variants associated with leukodystrophies. The LeukoGCEP is a collaborative effort with leukodystrophy experts from Children's Hospital of Philadelphia and Children's National Hospital in Washington, D.C. Visit clinicalgenome.org/affiliation/40107/ to learn more about the LeukoGCEP and see the group's progress so far.

National and International Organizational Efforts

Last year, **Dr. Amena Smith Fine** joined the ALD Connect Board of Directors. In this new position, she has shared proceedings of the adult ALD Patient-Focused Drug Development Meeting with the Food and Drug Administration at national and international conferences. She has also authored a manuscript on this topic to increase awareness of the challenges and unmet needs facing adults with ALD and their caregivers. At the 2024 annual meeting of ALD Connect, Dr. Smith Fine and the Moser Center's clinical research team provided attendees with an opportunity to participate in research on-site.

Dr. Smith Fine also joined Global DARE, the Adult Refsum Disease Medical and Scientific Advisory Board. Both ALD Connect and Global DARE are recipients of Chan Zuckerberg Initiative (CZI) Rare as One grants this cycle, which we expect will greatly expand the research networks and capacity of these organizations over the next four years.

Dr. Nemeth Mertz continues her tenure on the United Leukodystrophy Foundation (ULF) Medical and Scientific Advisory Board. This group meets yearly at the annual ULF meeting and throughout the year to discuss topics pertinent to the ULF and to review research projects eligible for funding. The ULF also hopes to fund trainees interested in a career in the leukodystrophies.

Wishing You All the Best for 2025!

Again, we reflect on the legacy of Dr. Moser—and what it means to the ALD community, to those of us who were fortunate to work alongside him, and to the generation of ALD clinicians and researchers who will continue to advance Dr. Moser's vision. This community is our family, and we strive to improve the lives of patients with leukodystrophies.

We'd like to offer you a sincere thank-you for continuing to believe in our mission. We'd be honored if you would consider making a contribution to the Moser Center, and we wish you all the best for 2025.