Moser Center for Leukodystrophies
at Kennedy Krieger Institute

2023 ADRENOLEUKODYSTROPHY RESEARCH UPDATE

Dear ALD Community,

We at Kennedy Krieger Institute hope this year-end report finds you and your family well. I would like to thank you for your trust and for the amazing contributions you have made in support of our adrenoleukodystrophy (ALD) research program. Not only did we receive financial donations, but, we are delighted to report, our patients continue to be interested in participating in research activities, providing us with their time and entrusting us to serve as their healthcare providers.

We continue to have a comprehensive ALD research program ranging from drug discovery in the dish to conducting clinical trials at the bedside, while also continuing to train and mentor the next generation of ALD researchers. I am fortunate to work with a strong team dedicated to improving the lives of patients with ALD. The basic research is led by Ann Moser and Dr. Christina Nemeth Mertz, while the clinical research is led by Dr. Amena Smith Fine, Dr. Jenn Keller, Dr. Gerald Raymond and our most recent recruits, who are listed below.

Dr. Eric Mallack

STAFFING UPDATES: We are delighted to announce several new additions to our Moser Center for Leukodystrophies team.

First, we have successfully recruited another nationally recognized ALD expert, Dr. Eric Mallack, for our team. Dr. Mallack joined us in October 2023 as the Moser Center's director of clinical research.

Dr. Mallack is an expert clinician-researcher and was the founding director of the Leukodystrophy Center at New York-Presbyterian/Weill Cornell Medical Center. His research focuses on advanced imaging techniques to understand neurodevelopment and early diagnosis of patients with cerebral ALD. He has complex care experience, including in the delivery of hematopoietic stem cell transplants, for patients affected by leukodystrophies. He previously served as the principal investigator for multiple clinical trials, including gene therapy trials. We recruited him specifically to reinstitute the stem cell transplant program in partnership with The Johns Hopkins Hospital and to increase the portfolio of clinical trials at Kennedy Krieger.

Lachelle Purnell-Savoy

We are excited to announce that Lachelle Purnell-Savoy, CRNP, joined us in June 2023 as a dedicated family nurse practitioner in the Moser Center. Lachelle brings her talents and experience as a former clinician in The Johns Hopkins Hospital's Diabetes and Metabolism Clinic, where she received the Johns Hopkins Advanced Practice Provider Appreciation Award before joining our team. She has taken an active role in our clinical research projects, evaluating patients for our natural history studies and clinical trials in ALD. She is quickly becoming a vital part of the team and provides comprehensive neurological care to both pediatric and adult patients with leukodystrophy in our clinic.

At the beginning of 2023, we were able to recruit Dr. Wedad Fallatah as our research program's inaugural Ann Moser Fellow. This fellowship is financially supported by the United Leukodystrophy Foundation, the Global Foundation for Peroxisomal Disorders, the Global DARE Foundation and the RhizoKids Foundation.

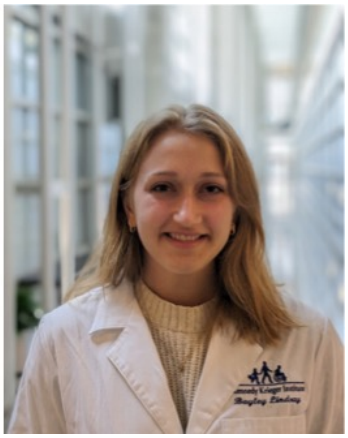
Dr. Wedad Fallatah

Dr. Fallatah holds a master's degree of advanced studies in clinical research from University of California San Diego and a doctorate in human genetics from McGill University. She studied medicine at King Abdulaziz University Medical College in Saudi Arabia. She is currently training directly under renowned researcher Ann Moser to learn the many biochemical skills Moser has developed over several decades.

We have also recruited two new research technicians and one new research coordinator to join our lab. Brett Ratajczak, a 2023 graduate of McDaniel College, joined us in June 2023, and Bayley Lindsay, a graduate of the University of Maryland, joined us in mid-summer of 2023. Both are working on basic research in the lab, where they study cell culture and animal models of ALD and other leukodystrophies. Dr. Bita Bozorgmehr, a pediatric geneticist by training with prior experience in other leukodystrophies, joined us in September 2023 as a new clinical research coordinator, assisting with clinical trials and natural history studies in ALD.

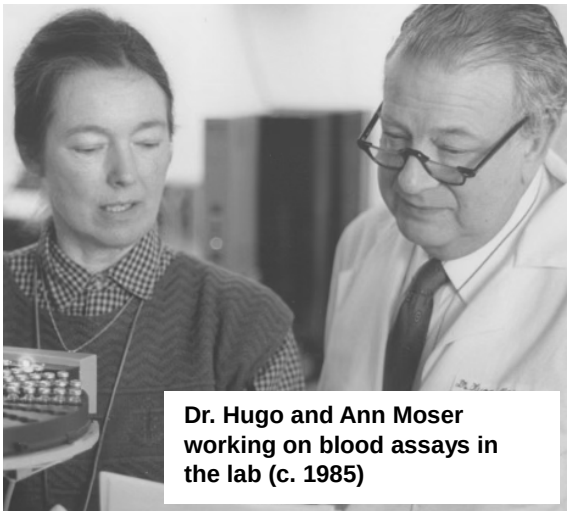
Dr. Bita Bozorgmehr

Brett Ratajczak



Bayley Lindsay

NEW CLINIC FOCUSING ON NEWBORN SCREENING: As newborn screening for ALD is expanding across the U.S., there is an unmet need for dedicated clinics to follow patients with a leukodystrophy identified at birth. Dr. Mallack, Purnell-Savoy and Julie Cohen, our director of genetic counseling, have launched the Leukodystrophy Newborn Screening Follow-Up Clinic (also known as the **LeukoNBS Clinic**) to provide care to newborn patients identified by newborn screening.



Dr. Hugo and Ann Moser working on blood assays in the lab (c. 1985)

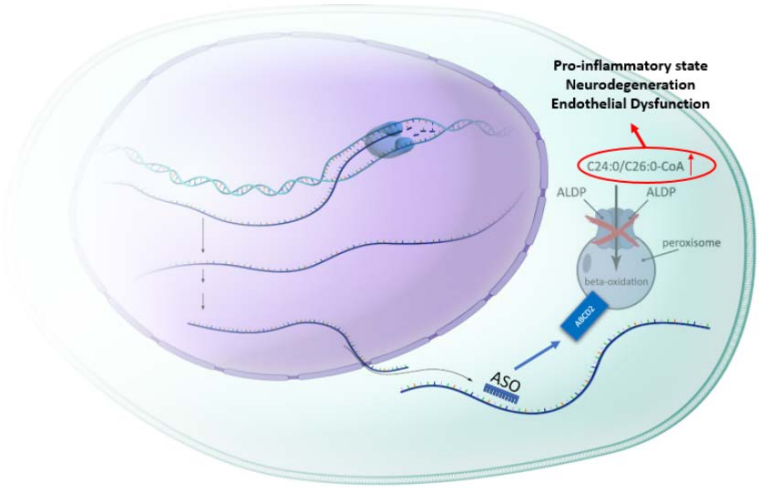
The LeukoNBS Clinic, which provides confirmation of genetics and diagnosis, expands family genetic testing, neurological and imaging surveillance, and rapid, early-stage referral for stem cell transplants or gene therapy, as clinically indicated. We are working with newborn screening labs across the U.S. to facilitate referrals to secure care for our patients.

Importantly, the assay used for newborn screening was developed here at Kennedy Krieger by Dr. Hugo and Ann Moser. It is extremely rewarding for us to see Dr. Moser's dream of early identification of and treatment for ALD becoming a reality today.

UNCOVERING DISEASE MECHANISMS AND DISCOVERING NEW THERAPIES FOR ALD: Despite a major breakthrough in lentiviral gene therapy in 2022, there are no approved disease-modifying therapies for the majority of individuals with ALD. We therefore continue our efforts to understand underlying disease mechanisms and identify new therapeutics in the lab to help address this very unmet need.

This year, we are pleased to report on new research from the lab exploring antisense oligonucleotides (ASOs) as a potential therapy for ALD. This work, conceived with the help of Dr. Manouchehr Amanat, a second-year postdoctoral research fellow in the lab, takes advantage of the many mechanisms of action of ASOs. These are small molecules developed in the lab that are built as mirror images of certain parts of our genes, allowing us to regulate the amount of the gene that is produced by each cell. ASOs have been approved by the Food and Drug Administration for a number of devastating diseases. ASOs are considered to be well tolerated, and they appear safe to use.

In ALD, the gene that is not functional is called *ABCD1*. It contains the instructions for a protein to transport very long chain fatty acids (called C24:0 and C26:0). The lack of functioning *ABCD1* results in impaired transport of these fatty acids, which in turn causes inflammation, degeneration of the nerve cells and damage to blood vessel cells (called endothelial cells). We developed an ASO that turns on a related gene, called *ABCD2*, which is very similar to *ABCD1* in its function and is usually turned off in our cells. By turning on *ABCD2*, the cells can transport the fatty acids and improve their metabolism (see illustration below).



New potential therapy for ALD: This antisense oligonucleotide (ASO) turns the *ABCD2* gene on to compensate for the impaired functioning of the *ABCD1* gene, thereby correcting the metabolic abnormality. We hope this therapy may slow down the inflammation and neurodegeneration experienced by people with ALD.

In the lab, when human ALD fibroblasts (derived from patient skin cells) in a dish are treated with three different ASOs (ASO1, ASO2 and ASO3) targeting the same region, production of *ABCD2* increases and very long chain fatty acids produced by the cells decrease. We presented this finding at the annual United Leukodystrophy Foundation meeting and the Annual Meeting of the Child Neurology Society this past year. Last winter, we published a review paper on ASOs. Visit ncbi.nlm.nih.gov/pmc/articles/PMC9695718/ to read the paper.

We are delighted that Dr. Amanat recently received a Young Investigator Award ($6,000) by ALD Connect to continue this project, and we are currently trying to obtain funding from the National Institutes of Health (NIH) to expand this therapeutic project to animal models and ALD patient-derived cell culture models.

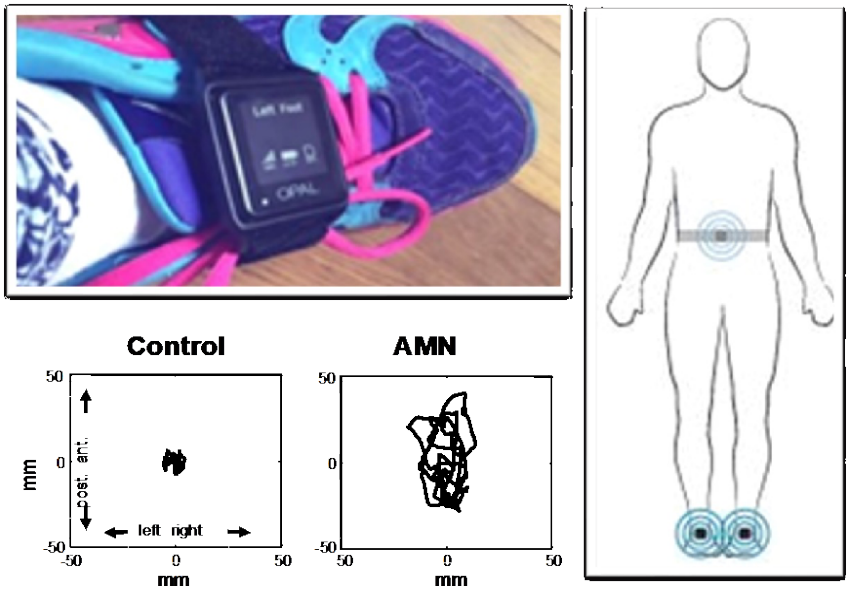
UNDERSTANDING DISEASE COURSE IN ADULTS WITH ALD: Since ALD is a rare disease, there are still many aspects of its course that remain unknown. For example, it is important to understand when disease in women and girls with ALD starts and how quickly symptoms progress. Additionally, there is a need for metrics that are both quantitative and meaningful, so they can be used to assess the effect of any therapy.

HARNESSING WEARABLE TECHNOLOGY AND ADVANCED NEUROIMAGING TO ASSESS PATIENTS FOR CLINICAL TRIALS: Dr. Smith Fine and the clinical research team at the Moser Center have continued to expand our multi-center, international research project using a wearable technology platform as a tool to remotely assess balance, walking speed and other gait measures in individuals with adrenomyeloneuropathy (AMN). Since 2019, this effort has been supported in part by a consortium grant funded by the NIH in

collaboration with Dr. Florian Eichler at Harvard University and Dr. Adeline Vanderver at Children's Hospital of Philadelphia.

Dr. Smith Fine deployed the wearable platform to evaluate walking and balance in a natural history study of ALD in 2021. These tests are performed both on-site, during clinic visits, and remotely, at patients' homes. So far, nearly 50 patients have been tested in person or remotely as part of this study, and many have had repeat testing every six to 12 months.

We have also established a strong collaboration in the last two years with our Dutch partners at Amsterdam Medical Center, led by Dr. Marc Engelen, who has adapted our research protocol using wearable sensors. We are submitting a manuscript this quarter on a combined data set from the U.S. and the Netherlands. In the paper, we report clinically meaningful relationships between sway and gait with falling frequency, use of an assistive device (cane or walker) and patient-reported quality of life.



OPAL wearable sensors placed on the trunk and both feet can detect the amount of sway present when a person tries to stand still. Note how a patient with adrenomyeloneuropathy (AMN) sways more than someone without AMN.

These measures may be well suited as primary outcomes for a clinical trial designed to assess the spinal cord and peripheral nerve involvement in ALD and to monitor disease progression in individual patients. Dr. Smith Fine will be reapplying for a five-year career development grant from the NIH in the spring of 2024 to extend her commitment to this project and support her collaboration with a group of computer and biomedical engineering specialists using artificial intelligence techniques to analyze wearables and MRI data. To this end, 20 patients with AMN and 15 volunteers without AMN from the project mentioned above have consented to undergo advanced quantitative brain and spinal cord MRI scans at baseline, and at one and two years after enrollment. Goals include determining if changes in these sequences correlate with sensorimotor changes tracked by the wearable sensors, and if we can predict the rate and nature of disease progression.

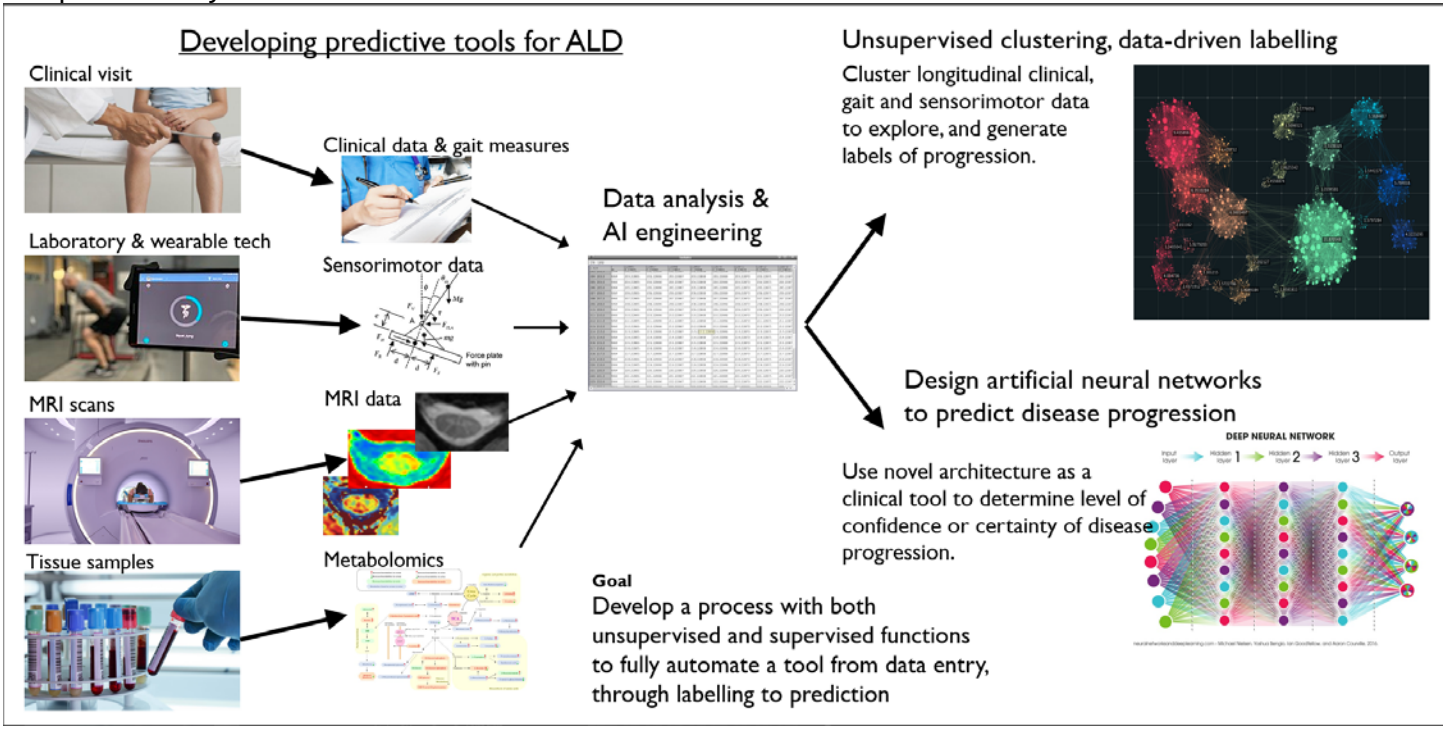
We are currently working on publishing the initial results of these studies. Importantly, as part of our commitment to the ALD community, we intend to share the research results with other investigators who are interested in understanding ALD.

In addition to the wearable technology studies, we are also conducting MRI studies and plasma biomarker studies to assess disease severity, and we are combining these results with cutting-edge machine-learning tools and using artificial intelligence in predicting disease course.

The hope is that one day, we may be able to use a small amount of blood to predict how fast a disease will worsen in an individual with ALD. The rationale behind this approach is based on the fact that we have identified several blood metabolites that appear to correlate well with neurological disability in our patients. We are now aiming to determine if these metabolites predict the future course of the disease. We use machine-learning tools that are able to discover relationships that traditional statistical tools cannot identify.

This work is led by Dr. Bela Turk, a postdoctoral research fellow in our lab, in close collaboration with Dr. Jaspreet Singh and Dr. Laila Poisson of Henry Ford Health in Detroit, Michigan. Together with Dr. Singh and our collaborators at the Global Leukodystrophy Initiative (GLIA) Consortium, we have submitted a request, still under review, for a large NIH grant. If we receive funding, we plan to study these machine-learning tools more

comprehensively.



BRINGING NEW THERAPIES TO ADULTS WITH ALD: We are participating in multiple early-phase clinical trials investigating novel small-molecule approaches to the treatment of adults with varying forms of ALD:

- **A Study to Assess the Pharmacodynamics of VK0214 in Male Subjects With AMN (recruiting): clinicaltrials.gov/study/NCT04973657**
- **A Clinical Study to Assess the Efficacy and Safety of Leriglitazone in Adult Male Subjects With Cerebral Adrenoleukodystrophy (recruiting): clinicaltrials.gov/study/NCT05819866**

If you are interested in learning more about these trials, please use the above-mentioned links. In the coming year, we plan to participate in additional clinical trials for ALD.

Also, Dr. Mallack is the principal investigator in a trial for children with early-stage cerebral ALD (European registration EudraCT Number: 2019-000654-59).

WISHING YOU ALL THE BEST FOR THE UPCOMING HOLIDAYS AND NEW YEAR!

As you can see, we have been very busy working on advancing disease research and providing better care to patients with ALD. The ALD community is our family, and there is nothing that matters more to us than improving the lives of patients with leukodystrophies. None of this could have been achieved without the teamwork of a fantastic **group of clinicians, nurses, researchers and trainees** dedicated to our work, and without our many national and international collaborators. At the Moser Center, we take an interdisciplinary approach, collaborating not just within the center, but with other specialists and scientists around the world to ensure that every one of our patients receives the best possible care, and in the hope that we find a cure for ALD.

I would like to take this opportunity to sincerely 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 a happy holiday season and all the best for 2024.***

Yours,

S. Ali Fatemi, MD, MBA
Director, Moser Center for Leukodystrophies
Chief Medical Officer, Kennedy Krieger Institute

To support the valuable research conducted by Dr. Fatemi and his research team, please consider making a secure donation online.

Gifts of all sizes are appreciated—you can make a difference!