Moser Center for Leukodystrophies
at Kennedy Krieger Institute

ALD 2022 Research Updates

STAFFING UPDATES

Our clinical team includes a total of 19 professionals who are evaluating patients at the Moser Center on a weekly basis. We evaluate around 100-150 individuals affected by ALD per year. We wished our long-term social worker, **Kiley Winstead,** a hearty goodbye in August of this year as she relocated for family reasons. Our clinic continues to receive social work support from **Bruce McClary**, who has had longstanding experience with leukodystrophy patients. **Dr. Christina Nemeth Mertz**, and our nurse practitioner, **Dr. Ayrowyn Tanner**, both welcomed new baby girls to their families this year.

On the research side, we have 16 professionals working on ALD. The research continues to be guided by the leadership of **Ann Moser, Dr. Amena Smith Fine**, **Dr. Christina Nemeth Mertz**, **Dr. Gerald Raymond** and myself.

DEVELOPING NOVEL THERAPEUTICS IN THE LAB

While gene therapy has been celebrated as a therapeutic strategy for ALD, so far it has only been shown to be effective in a subset of patients with ALD. Currently, there are no approved drugs for adrenomyeloneuropathy (AMN), females with ALD, or neurologically symptomatic patients with cerebral ALD.

At the Moser Center, we have developed several therapeutic strategies that are currently being tested in animals and in cell culture models of ALD. The ALD mouse, which lacks the ALD gene, known as *Abcd1*, has long been used to model the adult form of ALD, known as adrenomyeloneuropathy (AMN). Similar to patients, the ALD mouse develops elevation of very long chain fatty acids (VLCFA), which is the hallmark of ALD. In the laboratory, we are focusing on drugs that can increase the function of the ALD related protein, also known as ABCD2. This protein, ABCD2, has very similar function to ABCD1 and can reduce the elevated VLCFAs; however, ABCD2 is usually either turned off or has very low activity in most cells. The aim of our research is to increase ABCD2 through different drugs. Led by **Dr. Christina Nemeth Mertz,** we recently published a paper in which we use the nanoparticle conjugate dendrimer-4-phenylbutyrate as a drug to increase ABCD2, and we are currently working on obtaining funding to determine whether the potency can be improved by adding an antioxidant to the construct.

The mouse studies have been funded by the Brian's Hope Foundation and the many other generous donations we have received. We are very thankful for this financial support and trust in our work. We are in great need of research funding to continue similar work in the lab, and have submitted NIH grant proposals for future work using the dendrimer platform, which would

combine 4-phenylbutyrate with another drug that targets inflammation and oxidative stress. We believe that the combination of these different drugs through our nanoparticle delivery approach will likely have the most powerful impact on ALD.

Secondly, translating results from the laboratory into clinical trials is challenging in ALD, since the natural history of the disease is not well known and variable rates of disease progression make the unbiased assessment of therapies difficult. There is therefore a need to identify markers that can predict disease progression in advance, to allow stratification of the right set of research participants into trials. Finally, ALD affects people in all geographical areas, and frequent travel can hamper the enrollment of a sufficient number of research participants into trials. For this reason, here at Kennedy Krieger Institute, we have been focusing on:

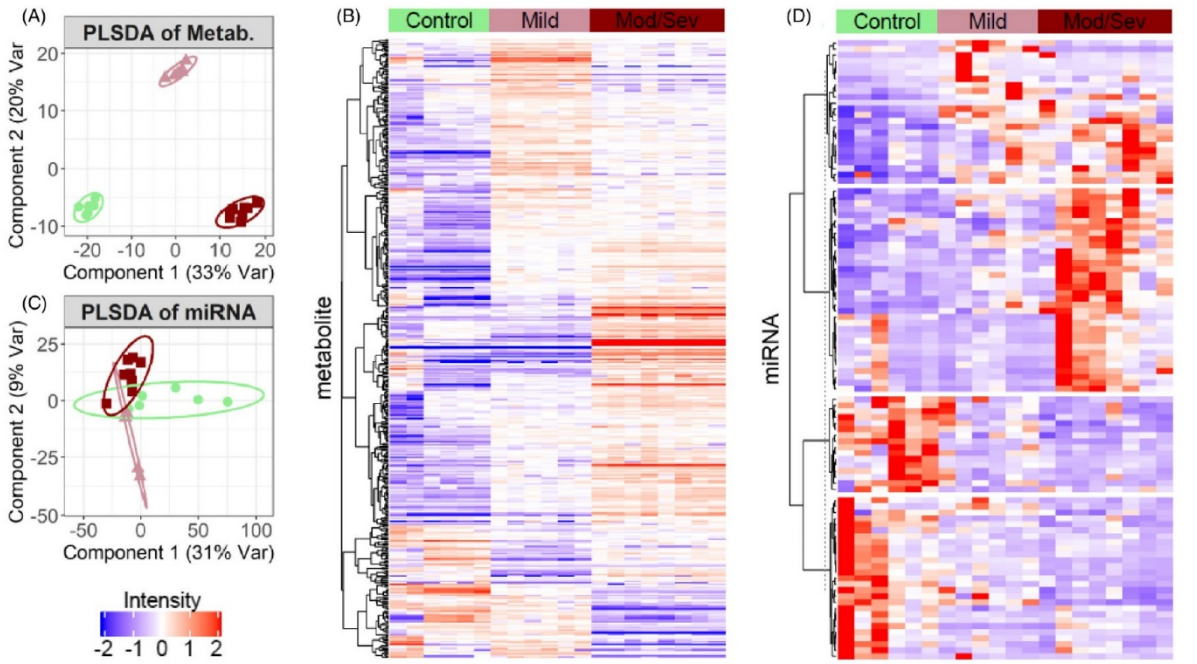
1) Developing approaches that allow delivery of therapeutics into the nervous system in a targeted manner.
2) Identifying biomarkers and imaging markers that predict disease progression in patients.
3) Remote assessment protocols using wearable technology to minimize travel.

Identifying Molecular and MRI-Imaging Predictors of Disease Progression

A major challenge in ALD research remains our inability to predict when the disease will start and what form of ALD an affected individual will develop. While newborn screening is extending quickly across the United States, we are looking for ways to determine which symptoms will progress, and the speed of progression in AMN.

Recently, we published the first molecular signature, differentiating healthy control, mild AMN and moderate/severe AMN using blood plasma. This molecular 'fingerprint' uses thousands of microscopic metabolites and micro-RNAs, and can clearly differentiate among disease severity. Additionally, our advances in machine learning and artificial intelligence approaches allow us to use these signatures to predict a patient's clinical severity score.

The figure below (A) shows how the green (control), pink (mild) and red (severe) AMN molecular signatures are similar within groups and differ from one another. This first step will help us develop tools to ultimately predict an individual's symptom progression and grant us insight into molecular mechanisms of AMN. Click here to view the publication.



We are continuing MRI scanning for AMN and healthy control individuals, using high-resolution anatomic and functional myelin imaging of the spinal cord to quantify the biochemical health of the nerve sheath. The continued goal of the MRI research is two-fold: First, to understand and develop markers of spinal cord health in AMN, and second, to integrate MRI imaging into the artificial intelligence (AI) tools being developed at the Moser Center.

Dr. Bela Turk has previously developed a series of AI applications for large data-sets, so far, including plasma biomarkers and clinical measures into the *'Moser Center Neural Network*' has shown a high grade of accuracy in experimentally predicting the trajectory of AMN symptom progression for research purposes. These networks have been developed in collaboration with a team of machine learning specialists at Johns Hopkins Malone Center for Computer Engineering in Healthcare, and a manuscript in preparation.

We are in need of funding to conduct a prospective study to determine whether these blood biomarkers, in combination with imaging, can predict the rate of progression of disease. This study would ideally be done to complement the studies using wearable technology. Together with Dr. Jaspreet Singh, at Henry Ford Health, we have applied to the NIH for several grants in the hopes of receiving funding to conduct this study.

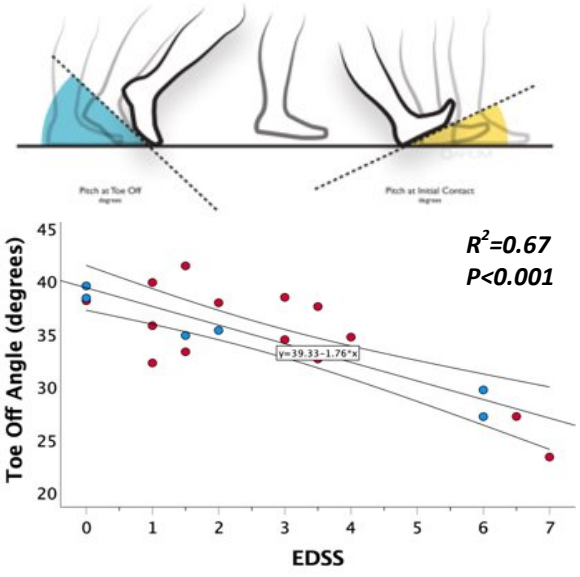
Harnessing Wearable Technology to Remotely Assess Patients in Clinical Trials

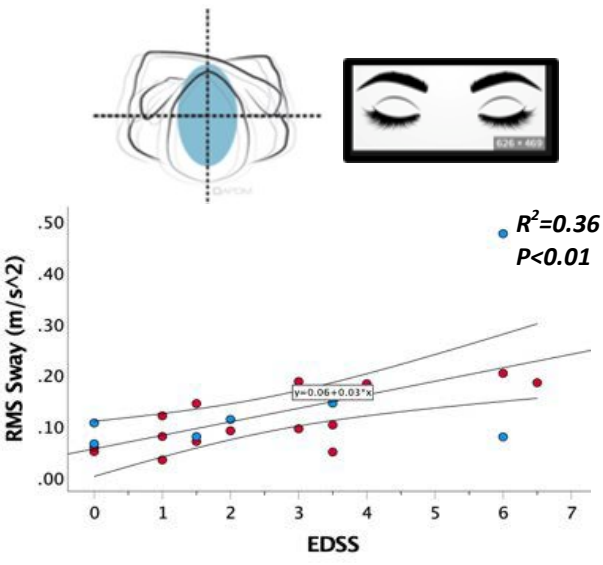
In 2017, in partnership with **Dr. Amy Bastian**, Chief Science Officer at Kennedy Krieger Institute, we began a new research project utilizing a wearable technology platform that had been used in Parkinson's Disease as a tool to remotely assess patients' balance, walking speed and other gait measures. In 2019, we were able to secure a consortium grant funded by the National Institutes of Health in collaboration with Dr. Florian Eichler at Harvard University and

Dr. Adeline Vanderver at Children's Hospital of Philadelphia, which provides us funding to conduct a longitudinal study in men and women with AMN using wearable technology and AI tools, and to remotely assess their gait dysfunction. **Dr. Amena Smith Fine** has deployed the wearable platform to evaluate walking and balance in a natural history study of ALD since February 2021. These tests are performed both on-site during clinic visits and remotely at patients' homes. So far, 25 patients have been tested in person or remotely as part of this study, and active enrollment is continuing over the next year. This work complements Dr. Smith Fine's ongoing projects using wearable technology to learn about disease progression in childhood-onset leukodystrophies.

OPAL sensor, kit and placement for testing gait and balance

Importantly, we have established a strong collaboration with our Dutch partners at the University of Amsterdam, led by Dr. Marc Engelen, who has adapted our research protocol, and have been collecting patient data both in the U.S. and in the Netherlands remotely using the same wearable technology. We have already identified a series of variables in common to our sites that depict abnormal patterns of gait and sway in AMN men and women at study baseline. In the below figures, the Toe Off Angle is strongly correlated with the disability score for women (red) and men (blue). This indicates impaired ability to push off the foot to start a step, which can be attributed to weakness or spasticity. The extent of sway while standing with the feet apart and eyes closed is also significantly correlated with the disability score. We are preparing a manuscript reporting these findings for submission in winter 2023. This data will be very useful for future clinical trials, which could be conducted at patients' homes or in the clinic setting, facilitating access to these trials.





In July 2021, **Dr. Smith Fine** was awarded a grant that supplements the above-mentioned NIH consortium grant and funds a portion of her faculty salary. She also applied for a five-year career development grant from the NIH in summer 2022, to extend her commitment to this project and support her collaboration with a group of computer and biomedical engineering specialists utilizing AI techniques to analyze wearables and MRI data. The grant was scored favorably, and we anticipate she will be able to secure funding upon re-submission of the application in spring 2023.

To make a gift in support of the valuable research conducted by Dr. Fatemi and his research team, please make a secure gift here.

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