UNITED LEUKODYSTROPHY FOUNDATION | VOL. 42 • NO. 1 • WINTER 2024

NEWSLETTER

CELEBRATE RARE DISEASE DAY IN STYLE!

Rare Disease Day was launched in 2008 to be celebrated on February 29th – the "rarest day on the calendar." On non-leap years, Rare Disease Day is observed on February 28th and some organizations will even extend their awareness campaigns to the entire month of February.

The ULF is proud to commemorate Rare Disease Day annually to represent the leukodystrophy community and its place in the larger rare disease community as a whole. **Here are some Rare Disease Facts to consider:**

- 72% of all rare diseases, including leukodystrophies, are genetic.
- 70% of genetic rare diseases start in childhood; for many years, leukodystrophies were primarily diagnosed in children until our understanding grew to include how leukodystrophies also affect adults.
- There are 7,000+ types of identified rare diseases; there are at least 50 different types of identified leukodystrophies and some studies suggest that number is closer to 90 as we continue to identify genetic variants leading to leukodystrophy diagnosis.
- 300 million people worldwide are living with a rare disease, which is nearly equivalent to the world's 3rd largest country by population.

ORDER YOUR
LIVING RARE
APPAREL AT:
Bonfire.com/LivingRare

Order by
Wednesday, February 7th
to receive your items in time to wear on February 29th!

If you miss the deadline, your items will arrive in March.

In 2024, we are asking the leukodystrophy community to highlight how they are Living Rare. You can do this by sharing your leukodystrophy story to spread awareness, donating to the ULF to support our mission, and by purchasing **Living Rare apparel** where a portion of the proceeds also benefits the ULF.

WHAT'S INSIDE

A LETTER FROM THE PRESIDENT OF THE BOARD

Welcome to our first newsletter of 2024. I hope that the new year has been kind to you all and you have managed to mostly avoid the worst of the many viruses that annually plague this time of year.

Ron, Marla, and their son Aiden

The dawning of another year always causes me to reflect upon the year just past and give thought to what I hope we can accomplish in the months ahead.

2023 was in many ways a landmark year for us at the ULF. Our conference back in June had the largest attendance in ULF history and was shared across all spectrums of our community. There were more researchers / clinicians, pharmaceutical companies, fellow advocacy groups and, most importantly, affected individuals and their families than ever before.

In September we brought aboard a new Executive Director, Diane Fennimore, to bring meaningful action towards addressing the many needs of our community. She is focused on raising awareness of these disorders among those not directly affected by a leukodystrophy. Doing so will bring in additional resources to support those of us who need a helping hand as well as extra funding which we direct towards research to further our understanding of these disorders and eventually find treatments and cures. September also saw us host a booth with several other leukodystrophy related advocacy groups at the premier conference in the rare disease world, NORD. Together we strived to make connections with potential new partners in the rare disease community and pharmaceutical companies, many of whom were still completely unaware of the leukodystrophies.

December saw us fund a grant, based on the recommendation of our Medical and Scientific Advisory Board (MSAB), from Dr. Daniel Segal out of Tel Aviv University. The grant will fund research aimed at identifying new potential targets within the brain for the treatment of Krabbe disease. Our MSAB feels there is the potential for this study to make a major difference in the treatment of not only Krabbe but other leukodystrophies as well. The fact that this grant was awarded to a new investigator from a part of the world that has not been traditionally heavily involved in researching these disorders made the decision even more rewarding. All in all, 2023 was a very good year for the ULF and we are looking to build upon this.

This promising new year starts with our annual Family Conference, slated for June the 28th and 29th, at the Eaglewood Resort in Itasca, Illinois, just a short 20 minute cab ride from O'Hare airport. Once again, attendees will have a chance to interact and ask questions of researchers and clinicians from across the U.S. and indeed around the world. The conference provides a unique opportunity to sit down for an extended amount of time and learn about new research that may still be unpublished from the very people who are conducting it. Unlike a traditional clinic appointment, there is no clock ticking as you speak. You can also hear from and speak to experts familiar with the leukodystrophies in such diverse fields as physiotherapy, diet, urology, fixing communication gaps and many other areas of need.

The hotel is a resort complete with a large family pool, a bowling alley, exercise facilities, a top golf course and food that is of 4-star quality. There will be care provided for kids - both with special needs and those without - with activities including games, arts and crafts and, of course, a visit to the bowling alley where the use of ramps and

staff allow even the most physically challenged among us to participate. The event costs are greatly subsidized by the ULF, allowing you to become both better informed about these diseases while enjoying a holiday of sorts that won't break the bank.

Our Ambassador program will role out this year, which should be a great aid in providing both a list of local resources as well as an experienced and caring ear that anyone with a leukodystrophy within their family can benefit from, but particularly those who are newly diagnosed. This year will also be a year that we reassess our strategic plan for the next few years to ensure we are meeting the community's changing needs.

Lastly, I would like to extend my thanks to the many who supported our foundation on Giving Tuesday and in their end of year donations. Your generosity support is greatly appreciated. I wish you all the best in 2024.

Best wishes to all,

RON CHAPLEAU

ULF Board President

WELCOME TO THE ULF'S NEWEST BOARD MEMBER!

Michele Herndon, St. Louis, Missouri

Michele Herndon, MSN, RN

Michele Herndon, MSN, RN, is the Program Director of the Undiagnosed Diseases Network Patient Navigation Program. Prior to this role, she worked for 18 years as a pediatric nurse, leader, and program manager at St. Louis Children's Hospital. She is also the co-founder and Vice-President of The Mitchell and Friends Foundation, an organization determined to support families and raise both awareness and money for research into an ultra-rare disease—Mitchell Syndrome.

A newly discovered disease, Mitchell Syndrome was named after Michele's oldest son, Mitchell, who died in 2019 at the age of 19. This ultra-rare neuromuscular disease has symptoms and imaging findings that are very similar to more well-known leukodystrophies. Mitchell was the first patient identified in 2018, the first journal article on the disease was published in 2020, and now the foundation is aware of nearly 30 patients worldwide. Michele is working with a team of researchers at Washington University School of Medicine to publish a retrospective natural history study on Mitchell Syndrome and develop treatments for the disease.

Michele and her husband live in St. Louis, MO. They have a daughter in high school, a son who recently graduated from college, and a lovely daughter-in-law! Michele is currently working to complete her Doctorate in Nursing Practice at the University of Missouri-Columbia with an anticipated graduation date of December, 2024.

For a full list of all of the ULF's Board of Directors, Medical and Scientific Advisory Board, and Staff, please visit: https://ulf.org/about-the-ulf/leadership/

RESEARCH GRANTS 2010–2023

Where your research donations go!

The ULF is honored to support scientific research through our annual Research Grant Cycle. Every October, we accept applications from around the world to push our knowledge of the leukodystrophies further. Over the past 14 years, the ULF has supported 28 projects and distributed over $715,000 in funds to promote faster diagnosis practices, improved therapies and new treatment options, and moving our community closer to a cure.

On the next pages, you will learn more about the project that the ULF has funded for the 2024 year, Dr. Daniel Segal of Tel-Aviv University and his work on Krabbe. The funds were distributed at the end of 2023 and reflect YOUR DONATIONS at work! Thank you to all who have donated to the ULF's research support efforts!

**Project funds with an asterisk designate a project that was funded with donations specifically allocated for that type of leukodystrophy.*

Year	Researcher	Institution	LD Type	Amount
2023	Daniel Segal	Tel-Aviv University	Krabbe	$33,000
2022	Cristina Cereda	ASST Fatebenefratelli Sacco, "V. Buzzi" Children's Hospital	AGS	$33,000
2022	Ann Moser	Kennedy Krieger Institute	Various	$20,000
2022	Marjo van der Knaap	Amsterdam UMC	VWM	$31,940*
2021	Vivi Heine	Amsterdam UMC	Cerebral ALD (cALD)	$30,000*
2021	Marjo van der Knaap	Amsterdam UMC	VWM	$38,000*
2020	Akshata Almad	Children's Hospital of Philadelphia	Aicardi-Goutieres Syndrome	$33,000
2020	Thomas Durcan	McGill University	Vanishing White Matter	$16,500
2020	Keith Van Haren	Stanford University Medical Center	Cerebral ALD (cALD)	$16,500
2019	Amer Alam	University of Minnesota	ALD	$33,000
2019	Joshua Bonkowsky	University of Utah	ALD	$13,000*
2019	Markus Hofer	University of Sydney, Australia	AGS	$33,000
2019	Paul Watkins	Kennedy Krieger Institute	ALD	$8,671*
2018	Alessandro Michienzi	University of Rome, Italy	AGS	$33,000
2018	Amy Waldman	Children's Hospital of Philadelphia	Alexander Disease	$33,000
2017	Ernesto Bongarzone	University of IL at Chicago	Krabbe	$33,000
2017	Reena Kartha	University of MN	ALD	$15,000*
2017	Mark Sands	Washington University (Kansas)	Various	$33,000
2017	Natasha Snider	University of NC at Chapel Hill	Alexander Disease	$33,000
2016	Tracy Hagemann	University of WI	Alexander Disease	$33,000
2016	Quasar Padiath	University of Pittsburgh	ADLD	$33,000
2016	Deborah Renaud	Mayo Clinic	AMN	$3,841
2015	Adeline Vanderver	Children's National Health System	Various	$20,000
2015	Weston Mille	University of MN	ALD	$6,000
2015	Ian Duncan	University of WI	PMD	$35,000
2014	Ian Duncan	University of WI	PMD	$35,000
2014	Fabrice Dabertrand	UVM College of Medicine	CADASIL	$25,000
2010	Phyllis Faust	Columbia University	Zellweger	$5,000

ULF'S MEDICAL & SCIENTIFIC ADVISORY BOARD

A Note from the MSAB

Hello Friends of the ULF! Every year the MSAB receives applications from around the world, highlighting the work behind how the world understands, diagnoses, and treats leukodystrophies. It has been a pleasure to see how these applications have evolve in recent years. Even 5 years ago most of our applications originated from institutions in the USA with only one or two from other countries. For the 2023 grant cycle, we saw the most diverse set of proposals yet, with scientists from Spain, the United Kingdom, Korea, Italy, the Netherlands, Israel, and the USA. We are heartened by this progression and global representation as it contributes to a successful future for the leukodystrophy research community.

The ULF's Medical and Scientific Advisory Board is made up of physicians and researchers from around the world that are the leading professionals in leukodystrophies today.

Every year, the MSAB gathers to review the grant applicants for the ULF's Research Cycle. For the 2023 award year, Dr. Keith Van Haren lead the consideration and review of each grant, and our entire MSAB weighed in with their thoughts of where the funds should go.

When the MSAB reviews grant applications, we consider their impact on the leukodystrophy community as a whole. We rank the applications based on scientific merit, which includes innovation, rigor of the proposed methods, and the potential impact of the work for the leukodystrophy community. Secondarily, we aim to prioritize funding for younger investigators who are just beginning to build their scientific programs and/or investigators that haven't previously or recently received funding from the ULF. Beginning last year, the MSAB adopted an National Institutes of Health (NIH)-style review process whereby each proposal is reviewed by three MSAB scientists with relevant expertise. Each reviewer reads and scores the proposals prior to a roundtable discussion with the entire MSAB. After each proposal is discussed, each MSAB member has a chance to score the proposal. The proposal with the highest score at the end of review is typically recommended for funding. This year applicants also received written feedback from their three primary reviewers so that they can use the reviewers' comments to improve their project in future application cycles. Once the MSAB chooses a grant they believe should be funded, they offer their recommendation to the ULF's Board of Directors for final approval. The Board of Directors reviews the recommended grant, the MSAB's feedback, and distributes the grant's funds in December.

When a project is funded through the ULF, the project funding begins the following calendar year. For example, our 2023 grant awardee will receive and use the ULF funds given during the 2024 calendar year. The following year, (i.e. 2025), the ULF will invite the investigator to present their funded work at the Scientific Symposium.

This year's proposals were excellent. The top scoring proposal impressed the reviewers with its unusual level of originality in its approach to understanding the disease mechanisms in Globoid Cell Leukodystrophy (also known as Krabbe disease), a long-studied leukodystrophy. Reviewers were also optimistic about the potential to shed new insight into similar disease mechanisms for other neurometabolic disorders.

The ULF and the MSAB are thrilled to announce that the 2023 Research Grant recipient is Dr. Daniel Segal of Tel Aviv University in Israel and his project titled "Amyloid self-assemblies of sphingolipids - pathogenic agents in Globoid Cell Leukodystrophy." You can read more about Dr. Segal's project and how it hopes to impact our knowledge of Krabbe disease and beyond in this newsletter.

Thank you to all the supporters of the ULF who have made this funding opportunity possible! Funding groundbreaking research like Dr. Segal's simply wouldn't be possible without you. Progress begins with you.

Sincerely,

Keith Van Haren

Keith Van Haren MD
kpv@stanford.edu
Assistant Professor, Department of Neurology & Pediatrics | Stanford University School of Medicine
Tashia and John Morgridge Endowed Faculty Scholar in Pediatric Translational Medicine | Stanford Maternal & Child Health Research Institute

RESEARCH SUMMARY: 2023 GRANT AWARD WINNER

Amyloid self-assemblies of sphingolipids - pathogenic agents in Globoid Cell Leukodystrophy

Dr. Daniel Segal, Tel Aviv University

Recent results from our lab suggest that galactosylceramide (GalCer) and galactosylsphingosine (GalSph, a.k.a. psychosine) which accumulate in Globoid Cell Leukodystrophy as a result of a mutation in the GALC gene, can form unique toxic clumps, and as such may constitute novel therapeutic targets.

We have previously discovered that a related compound, galactosylceramide, which accumulates in Gaucher disease, can self-assemble in the test tube into highly ordered fibrils that greatly resemble the infamous amyloid fibrils that are the protein culprits of various neurodegenerative diseases, such Amyloid-beta in Alzheimer's disease and alpha-synuclein in Parkinson's disease. We further demonstrated that the amyloid-like self-assemblies of galactosylceramide are toxic to cell culture and are found in cells derived from Gaucher patients. Interestingly, we found that these fibrils can promote formation of alpha-synuclein fibrils, and thus may account for the prevalence of Parkinson's disease among Gaucher patients. Importantly, we discovered that certain small molecules, which are known as inhibitors of amyloid formation, are capable of mitigating the self-assembly of glucosylceramide in the test tube and in cell culture.

Dr. Daniel Segal and Dr. Sourav Kumar
photo provided by Dr. Segal

Our ULF supported project is based on our recent observations that GalCer and GalSph can also self-assemble in the test tube to form comparable amyloid-like fibrils. We plan to: substantiate these preliminary observations by various biophysical approaches; examine if we can observe GalCer and GalSph fibrils in cell-culture models of Globoid Cell Leukodystrophy using a combination of immunological and microscopical detection methods and test their noxious effect towards cells using biochemical and molecular tools; employ biophysical methods to assess whether the GalCer and GalSph fibrils can promote formation of alpha-synuclein fibrils; and begin to investigate several candidate small molecules for their ability to prevent the self-assembly of GalCer and GalSph into fibrils and to dismantle already-formed fibrils.

If successful, this research will identify novel pathogenic agents of Globoid CellLeukodystrophy, namely amyloid-like self-assemblies of GalCer and GalSph accumulated in the cells of the patients. Further, it will provide detailed biophysical information regarding their structure and mode of self-assembly which will be useful for planning their mitigation. It will also shed light on their pathogenicity as a component of the pathology of Globoid Cell Leukodystrophy. Finally, this research may identify a novel class of potential therapeutics for Globoid Cell Leukodystrophy, namely amyloid inhibitor small molecules. This could lead in the future to validation of these candidate molecules, and their improvement by medicinal chemistry, in available mouse models of Globoid Cell Leukodystrophy, in preparation for clinical trials.

SAVE THE DATE
2024 CONFERENCE

SCIENTIFIC SYMPOSIUM • JUNE 27

FAMILY CONFERENCE • JUNE 28/29

Eaglewood Resort and Spa • Itasca, Illinois, USA

Scientific Symposium: Thursday, June 27

For members of our medical professional and industry community, the Scientific Symposium offers the latest research from around the world. We recommend attendees arrive on Wednesday, June 26 as sessions begin at 8 AM on Thursday morning.

Family Conference: Friday, June 28 and Saturday, June 29

All are welcome! Affected families, caregivers, medical professionals, researchers, allied supporters and advocates, and anyone who would like to learn about living with leukodystrophies.
We recommend attendees arrive on Thursday, June 27 and join us for the kick-off dinner at the Eaglewood Red Oak Ballroom. Sessions begin at 9 AM on Friday, June 28.

Registration opens soon, but you can book your room today!

Book your room at **bit.ly/ulf2024** (case sensitive)
or by scanning the QR code

Learn more at ULF.org/Conference

224 North Second Street, Suite 2
DeKalb, IL 60115 | www.ulf.org

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SEE PAGE 7 FOR DETAILS