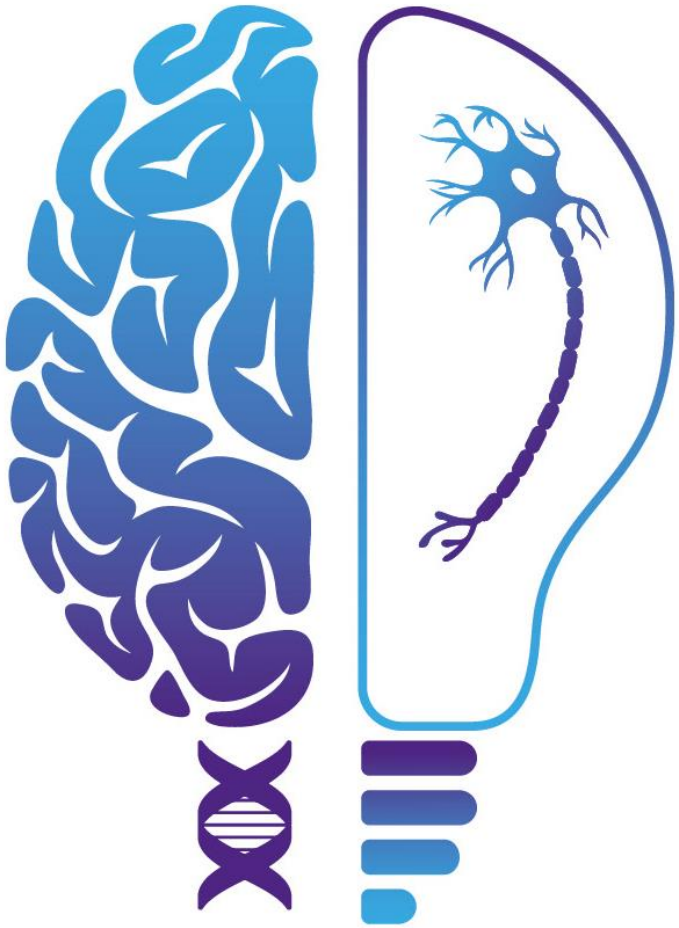


MyeliNeuroGene

LAB

2024 REPORT

Dr. Geneviève Bernard

Dr. Geneviève Bernard

MD, MSc, FRCPC

Dr. Bernard has built an internationally renowned comprehensive and cohesive **translational research program on leukodystrophies (LDs)** from bedside, to bench, to bedside, to develop targeted therapies that benefit her patients. Her research program is the **only one of its kind in the country**. She pioneered the **first LD clinic in Canada at the Montreal Children's Hospital**, where Canadian and international families are evaluated using a multidisciplinary approach tailored to their specific complex care needs. Access to this clinic and her **unique clinical expertise** have allowed families to obtain proper diagnoses, genetic counseling, supportive care, and an opportunity to participate in her research program. The recognition of the state-of-the-art care provided to these families contributed to her receiving the **Specialist of the Year Award of the Canadian Royal College of Physicians and Surgeons in 2019**. Her scientific productivity has solidified her status as an **international leader** in the LD field, bolstered by **collaborations with esteemed international experts**. The continuous expansion of her research program to add novel clinical and basic science facets is driven by the knowledge gaps she identifies when caring for these patients. Notably, her international leadership played a significant role in her receipt of the **2020 Maude Abbott Prize**, which recognizes McGill University female faculty at an early career stage who have excelled and demonstrated great leadership in education, research, or administration, as well as the **2023 Pfizer Research Award of Excellence**. Most recently, she was honored with the **2023 Moser Service Award from the United Leukodystrophy Foundation (ULF)** for outstanding service and commitment to the lives of people with LD and their families, and the **2024 Award "Les Grands Amis d'Élliot",** which is presented to those who, through their dedication, have contributed to the success of the Fondation des Amis d'Élliot over the years.

Her work has led to the **identification of 8 novel genes**, and the clinical and radiological characterization of ***POLR3*-related LD (*POLR3*-HLD)**, one of the most common LDs, leading to the ground-breaking understanding of its disease pathogenesis. This has allowed her to initiate the development of small molecules and gene therapies. Dr. Bernard has led the **4 largest international clinical, radiological, and molecular studies on *POLR3*-HLD**, was the first to unravel disease pathogenesis and to develop a representative mouse model of the disease. Her publication record includes more than **150 manuscripts** in impactful internationally recognized journals.

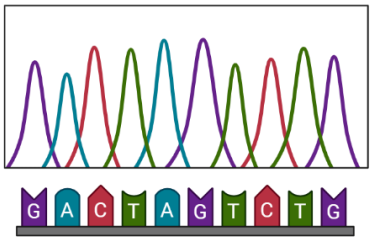
Dr. Bernard has held **uninterrupted salary awards**: the 2025-2029 Distinguished Research Scholars (FRQS Chercheurs-Boursiers de Mérite Award), Fonds de Recherche du Québec – Santé (FRQS) Clinical Research Scholars Junior 1, CIHR New Investigator, FRQS Senior and 'Chercheur de Mérite' salary awards. Notably, she ranked first in both the FRQS Clinical Research Scholars Junior 2 (declined) and Senior applications. Finally, Dr. Bernard is co-Director of RARE.QC, a rare disease consortium funded by the FRQS (2.7M, 2024-2028) and PI and member of the executive committee of RareKids-CAN, the Pediatric Rare Disease Clinical Trials and Treatment Network funded (20M. 2024-2029) by CIHR. Recently, she has also created and led the **CARELeuko Network**, an initiative that will connect Canadian specialists together to advance the field of leukodystrophy research. Dr. Bernard is the **Chair of the Medical and Scientific Advisory Board of the ULF**, one of the largest LD foundations in the world. She is the first woman, first Canadian, and youngest individual in this position. She also sits on the **Pelizaeus-Merzbacher Disease Foundation Scientific Advisory Board** and the **Yaya Foundation Scientific and Clinical Advisory Council**. Dr. Bernard also participates and presents in family conferences/family organizations' fundraising events yearly.

Dr. Bernard sits at the **crossroads of LD clinical practice and research**. It is clear that she has the ability to **leverage her large and expanding cohort of patients, international recognition, and large network of collaborators,** to translate the results of her studies into clinical protocols, benefitting patients in **real time**.

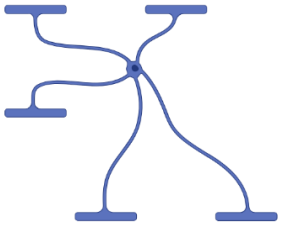
Dr. Bernard's Research Program on Leukodystrophies

Dr. Bernard has developed a comprehensive and cohesive research program focused on **leukodystrophies**. Leukodystrophies are a group of **rare genetic diseases** that affect previously healthy children and lead to **progressive disabilities** and premature death. They are caused by abnormalities in **myelin** (white matter), which is a protective sheath around neurons (brain cells) that ensures rapid nerve signal conduction. Neurons can be compared to electrical wires, where myelin is the rubbery insulation that protects them and facilitates fast electrical conduction.

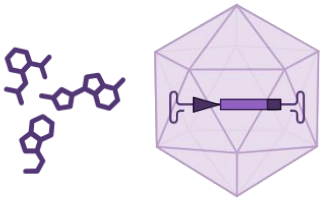
Dr. Bernard's research program aims to address the **following challenges**:



20-30% of patient remain without a molecular diagnosis



Pathophysiology of recently described LDs is poorly understood



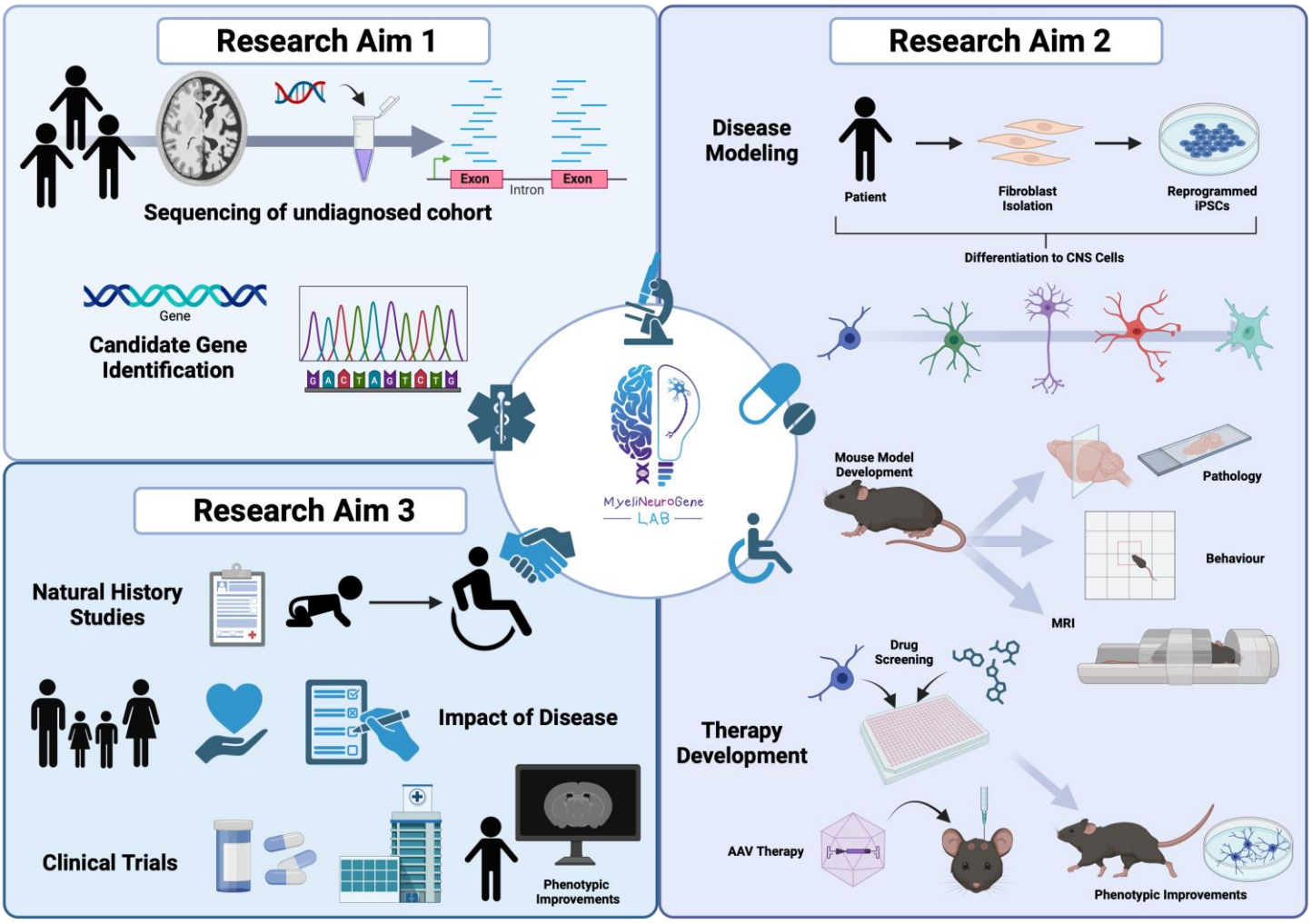
Most LDs do not have disease-modifying therapies

Natural history data and surrogate disease markers to evaluate therapeutic efficacy are lacking

Data on patient- and family-reported outcomes of disease impact are limited

Evidence-based guidelines for the care of affected children do not exist

To address these challenges, her research program is divided into three aims. The **first project** utilizes advanced DNA sequencing technologies to identify new causative genes. The **second project** focuses on understanding the pathophysiology of 4H leukodystrophy and *EPRS1*-related leukodystrophy. She employs the use of patient-derived stem cells and mouse models to explore the mechanisms of these disorders, and aims to both identify and test new potential treatments, including small molecules and gene therapies. The **third project** aims to study the natural history of leukodystrophies and identify clinical symptomatology criteria for use in therapeutic trials. This project also involves assessing the burden these diseases have on patients and their families to improve the care provided to them. Finally, this third project involves her participation as an investigator in therapeutic trials initiated by pharmaceutical and biotechnology companies, as well as her own led clinical trials.



Meet Our Research Staff

Laura Lentini, MSc
Clinical Research Coordinator
Project: Stress and Quality of Life of Parents of Children with *POLR3*-related Leukodystrophy

Adam Le, MSc
Clinical Research Coordinator
Project: *POLR3*-related Leukodystrophy: A Qualitative Study on Parents' Experience with the Health Care System and Burden of Disease in Parents and Siblings

Dr. Xiaoru Chen, PhD
Research Associate
Project: Generation and characterization of POLR3-HLD mouse models

Dr. Chia-Lun Wu, PhD
Research Associate
Project: Evaluation of an AAV Gene Replacement Therapy in a Polr3b Mouse Model

Meet Our Post-Doc and PhD. Students

Dr. Sabrina Alam, PhD
Post-Doctoral Fellow
Project: Development and characterization of leukodystrophy mouse models, and pre-clinical testing of potential therapeutics

Mack Mitchell-Robinson, BSc *MD/PhD Candidate*
Project: Investigating the role of RNA polymerase III subunit mutations in the development of hypomyelinating leukodystrophy and genetically related disorders

Alexandra Chapleau, BSc
PhD Candidate
Projects: *EPRS1*-related leukodystrophy clinical, genetic, and pathophysiological characterization using patient-derived iPSCs

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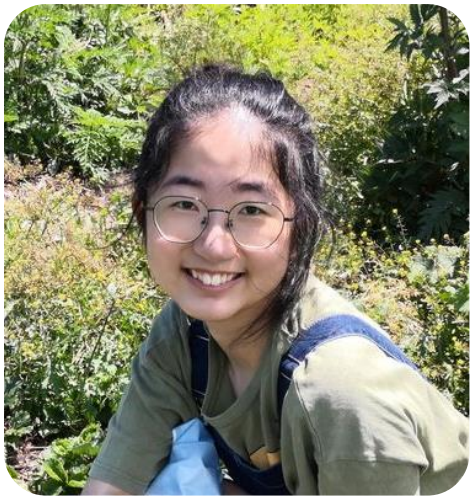
Meet Our Graduate Students

Bryan Inibhunu, BSc
MSc Candidate
Project: *POLR3*-related leukodystrophy: The role of astrocytes in disease pathogenicity

Samuel Gauthier, BSc
MSc Candidate
Project: Preclinical Assessment of Antisense Oligonucleotide Therapy for RNA Polymerase III-Related Leukodystrophy using Brain Organoids

Batool Hassan, BSc
MSc Candidate
Project: Preclinical testing of Riluzole therapy in *POLR3*-related leukodystrophy



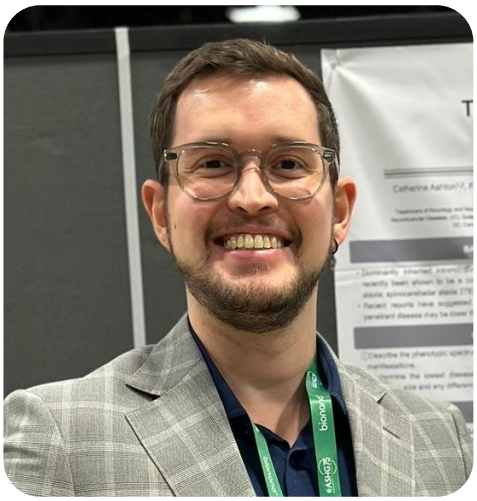
Jiayue Yin, BSc
MSc Candidate
Project: Exploring the Pathophysiology of POLR3-HLD: Generation of an iPSC-based Model from Patients with Biallelic Pathogenic Variants in POLR1C

Zahra Kazemi, BSc
MSc Candidate
Project: Fibroblast Profiling in POLR3-Related Leukodystrophy: A Platform for Testing New Therapeutic Strategies

Meet Our Medical Residents and Fellow

Dr. Gabrielle Lambert, MD
Medical Resident
Project: Natural History Study of the Striatal Form of *POLR3*-related Leukodystrophy

Dr. Quentin Sabbagh, MD
Visiting Medical Resident
Project: Identification of new candidate genes responsible for leukodystrophies



Dr. Felipe Villa Tobon, MD
Neurogenetics Fellow
Projects: *EPRS1*-related leukodystrophy: genotype-phenotype correlation; Natural History Study of the Striatal Form of *POLR3*-related Leukodystrophy

Meet Our 2024 Volunteers and Summer Students!

Kelly-Ann Thibault,
Medical Student

Projects: The Impact of *POLR3*-related Leukodystrophy on Non-affected Family Members: A Qualitative Study; Rare diseases: assessment of the impact of knowledge translation on patients and their families

Anne Michèle Laperrière,
CÉGEP Student

Alix Rommel,
BSc Candidate

Mina Hmimas,
Medical Student

Edina Lu,
CÉGEP Student

WET LAB RESEARCH

MyeliNeuroGene LAB

Polr1c Mouse Model Development

Through the methodologies used in the development of our *Polr3b* mouse model, our lab is now shifting focus to develop a *Polr1c* mouse model to better understand the disease mechanisms.

Preclinical Therapy Testing in Animal models

This project's objective is to test novel therapeutics (such as the gene therapy and an FDA approved drug Riluzole) using the *Polr3b* mouse model to see how these therapeutics interact within the disease model.

Induced Pluripotent Stem Cell (iPSC) Disease Modeling

The aim of this project is to use patient-derived iPSCs to generate various neurological cell types to better understand how these disorders impact the brain on a molecular level.

CLINICAL RESEARCH

MyeliNeuroGene LAB

Qualitative Study Exploring the Experience of Parents of Children with *POLR3*-related Leukodystrophy Navigating the Healthcare System

This project aims to understand the experience of parents of children with 4H leukodystrophy navigating the healthcare system, looking into factors of time, travel, financial challenges, and family dynamics.

Stress and Quality of Life of Parents of Children with *POLR3*-related Leukodystrophy

The goal of this project is to explore the quality of life, stress, coping mechanisms and experiences of parents of children with 4H leukodystrophy, both on a short and long-term basis throughout their child's disease progression.

Natural History Study of the Striatal Form of *POLR3*-related Leukodystrophy

The aim of this study is to collect longitudinal data of the striatal form of POLR3-HLD to better characterize its clinical spectrum, major milestones, associated morbidities, complications, and outcomes. This will facilitate the estimation of the disease progression, improve current standards of care, and identify novel biomarkers to eventually monitor treatment response in future clinical trials.

Exploring the Impact of Rare Disease Support Interventions for Patients and their Families

This project's objective is to determine how educational materials (such as information brochures) or conferences focusing on rare disease may improve quality of life of families by giving insight into their child's disease.

SELECTED PUBLICATIONS

Case Reports > Front Neurol. 2023 Oct 13:14:1254140. doi: 10.3389/fneur.2023.1254140. eCollection 2023.

Biallelic pathogenic variants in *POLR3D* alter tRNA transcription and cause a hypomyelinating leukodystrophy: A case report

Julia Macintosh [1 2], Stefanie Perrier [1 2], Maxime Pinard [3], Luan T Tran [1 2], Kether Guerrero [1 2], Chitra Prasad [4 5 6], Asuri N Prasad [4 6], Tomi Pastinen [7 8 9], Isabelle Thiffault [7 8 10], Benoit Coulombe [3 11], Geneviève Bernard [1 2 12 13 14]

Affiliations + expand

PMID: 37915380 PMCID: PMC10616956 DOI: 10.3389/fneur.2023.1254140

> Brain. 2023 Dec 1;146(12):5070-5085. doi: 10.1093/brain/awad249.

Hypomyelination, hypodontia and craniofacial abnormalities in a Polr3b mouse model of leukodystrophy

Mackenzie A Michell-Robinson [1 2], Kristin E N Watt [3], Vladimir Grouza [1 4], Julia Macintosh [1 2], Maxime Pinard [5], Marius Tuznik [1 4], Xiaoru Chen [1 2], Lama Darbelli [1 2], Chia-Lun Wu [1 2], Stefanie Perrier [1 2], Daryan Chitsaz [1], Nonthué A Uccelli [1], Hanwen Liu [1 4], Timothy C Cox [6], Christoph W Müller [7], Timothy E Kennedy [1], Benoit Coulombe [5 8], David A Rudko [1 4 9], Paul A Trainor [3 10], Geneviève Bernard [1 2 11 12 13]

Affiliations + expand

PMID: 37635302 PMCID: PMC10690025 DOI: 10.1093/brain/awad249

> Front Neurosci. 2023 Apr 25:17:1167047. doi: 10.3389/fnins.2023.1167047. eCollection 2023.

Decreased RNA polymerase III subunit expression leads to defects in oligodendrocyte development

Julia Macintosh [1 2], Mackenzie Michell-Robinson [1 2], Xiaoru Chen [1 2], Geneviève Bernard [1 2 3 4 5]

Affiliations + expand

PMID: 37179550 PMCID: PMC10167296 DOI: 10.3389/fnins.2023.1167047

> MethodsX. 2023 Feb 2:10:102051. doi: 10.1016/j.mex.2023.102051. eCollection 2023.

An optimized and validated protocol for the purification of PDGFRα+ oligodendrocyte precursor cells from mouse brain tissue via immunopanning

Julia Macintosh [1 2], Mackenzie A Michell-Robinson [1 2], Xiaoru Chen [1 2], Daryan Chitsaz [1 3], Timothy E Kennedy [1 3], Geneviève Bernard [1 2 4 5 6]

Affiliations + expand

PMID: 36814689 PMCID: PMC9939712 DOI: 10.1016/j.mex.2023.102051

> J Child Neurol. 2023 Apr;38(5):329-335. doi: 10.1177/08830738231176672. Epub 2023 May 24.

The Experience of Parents of Children With Genetically Determined Leukoencephalopathies With the Health Care System: A Qualitative Study

Pouneh Amir Yazdani [1 2 3 4], Marie-Lou St-Jean [1 2 3 5], Sara Matovic [1 2 3], Aaron Spahr [1 2], Luan T Tran [1 2], Renée-Myriam Boucher [6], Chantal Poulin [2 3], Bradley Osterman [2 3], Myriam Srour [1 2 3], Bernard Rosenblatt [2 3], Sébastien Chénier [7], Jean-Francois Soucy [8 9], Anne-Marie Laberge [8 9], Maria Daniela D'Agostino [10 11], Cam-Tu Emilie Nguyen [12], Maxime Morsa [5 13], Geneviève Bernard [1 2 3 10 11]

Affiliations + expand

PMID: 37225698 PMCID: PMC10338692 DOI: 10.1177/08830738231176672

> Front Neurol. 2023 Apr 3:14:1148377. doi: 10.3389/fneur.2023.1148377. eCollection 2023.

Solving inherited white matter disorder etiologies in the neurology clinic: Challenges and lessons learned using next-generation sequencing

Stefanie Perrier [1 2], Kether Guerrero [1 2], Luan T Tran [1 2], Mackenzie A Michell-Robinson [1 2], Geneviève Legault [1 2 3], Bernard Brais [1 4 5], Michel Sylvain [6], James Dorman [7 8], Michelle Demos [9], Wolfgang Köhler [10], Tomi Pastinen [11 12], Isabelle Thiffault [11 12 13], Geneviève Bernard [1 2 3 5 14]

Affiliations + expand

PMID: 37077564 PMCID: PMC10108901 DOI: 10.3389/fneur.2023.1148377

> J Med Genet. 2023 Oct;60(10):1026-1034. doi: 10.1136/jmg-2023-109223. Epub 2023 May 16.

Craniofacial features of POLR3-related leukodystrophy caused by biallelic variants in *POLR3A*, *POLR3B* and *POLR1C*

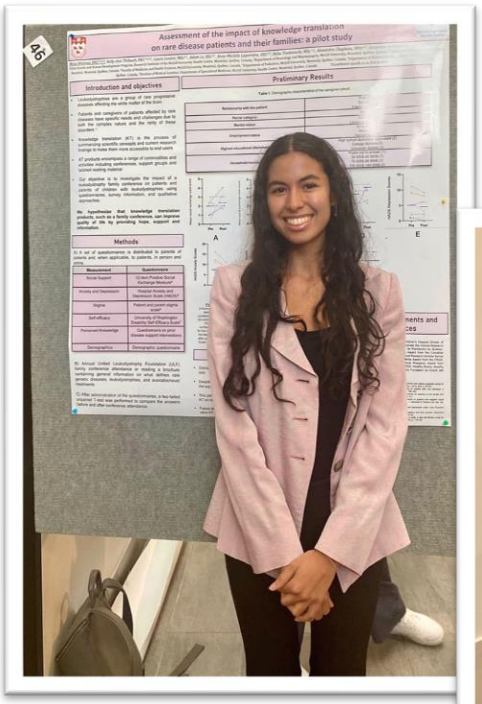
Amytice Mirchi [# 1 2 3], Simon-Pierre Guay [# 4 5], Luan T Tran [1 3], Nicole I Wolf [6], Adeline Vanderver [7 8], Bernard Brais [1 4 9], Michel Sylvain [10], Daniela Pohl [11], Elsa Rossignol [12], Michael Saito [13], Sebastien Moutton [14], Luis González-Gutiérrez-Solana [15], Isabelle Thiffault [16 17], Michael C Kruer [18 19 20], Dolores Gonzales Moron [21], Marcelo Kauffman [22], Cyril Goizet [23 24], László Sztriha [25], Emma Glamuzina [26], Serge B Melançon [27], Sakkubai Naidu [28], Jean-Marc Retrouvey [29], Suzanne Lacombe [29], Beatriz Bernardino-Cuesta [30], Isabelle De Bie [# 4 5 31], Geneviève Bernard [# 32 2 3 4 5]

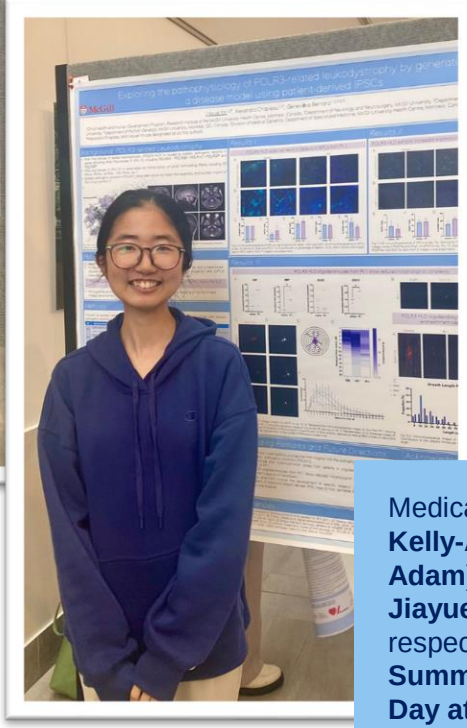
Affiliations + expand

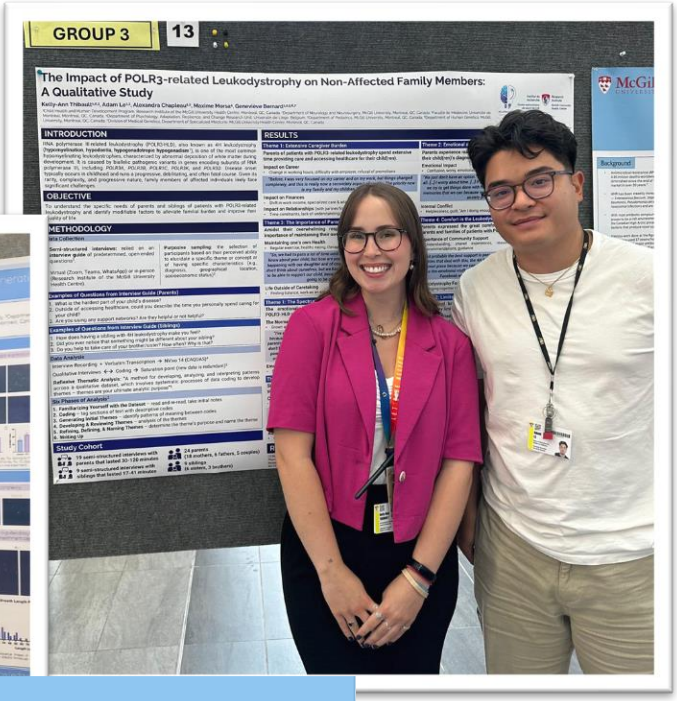
PMID: 37197783 PMCID: PMC10579516 DOI: 10.1136/jmg-2023-109223

For a more thorough review of **all 2023-2024 publications** by Dr. Bernard and her team, please scan the QR code!

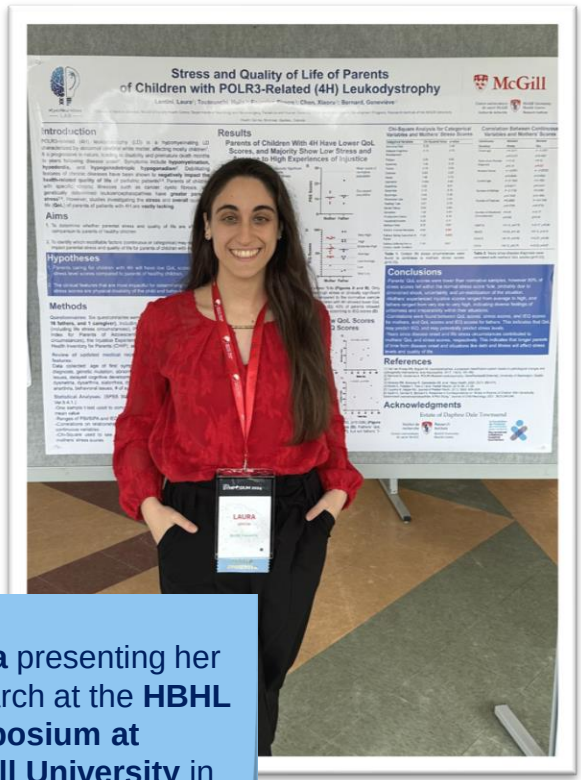
BERNARD LAB CONFERENCE PRESENTATIONS



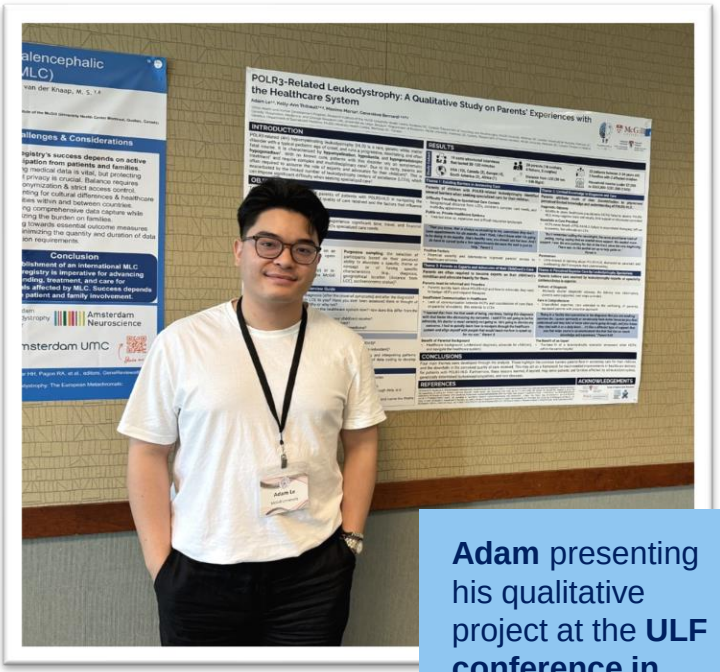




Medical students **Mina** and **Kelly-Ann** (with her mentor **Adam**), and MSc student **Jiayue,** presenting their respective posters at the **Summer Student Research Day at the RI-MUHC** in *August 2024*



Laura presenting her research at the **HBHL Symposium at McGill University** in *May 2024*



Adam presenting his qualitative project at the **ULF conference in Itasca, Illinois** in *June 2024*

2024 Bernard Team Research Awards!

Alexandra Chapleau, *PhD Student*

- Holds **CIHR CGS-D and FRQS Doctoral Training Scholarships**
- Won **1st place poster at Congrès Mère-enfant 2023**
- Awarded **Canadian Stem Cell Network International Travel Award**
- Won **best student oral presentation** for the CHHD PhD program

Adam Le, *MSc Candidate*

- Holds the **IPN Internal Student Award**
- Won **1st prize at CHHD Research Day 2024** for his junior poster presentation
- Won **3rd place at RareDIG Rare Disease Day 2024** for his poster presentation

Samuel Gauthier, *MSc Candidate*

- Awarded **CIHR CGS-Masters**
- Awarded the **RI-MUHC Studentship**
- Won **1st place poster at the RI-MUHC Research Day 2024**

DR. BERNARD IN THE MEDIA

Centre universitaire de santé McGill
Institut de recherche

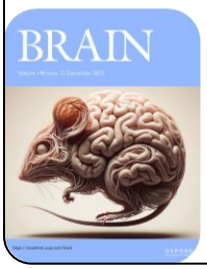
McGill University Health Centre
Research Institute

Major scientific achievement gives hope to families affected by 4H leukodystrophy

September 13th, 2023 NEWS RESEARCH RELEASES

RI-MUHC team creates first representative model of this rare disease

https://muhc.ca/news-and-patient-stories/news/major-scientific-achievement-gives-hope-families-affected-4h



JOURNAL ARTICLE

Hypomyelination, hypodontia and craniofacial abnormalities in a *Polr3b* mouse model of leukodystrophy

Mackenzie A Michell-Robinson, Kristin E N Watt, Vladimir Grouza, Julia Macintosh, Maxime Pinard, Marius Tuznik, Xiaoru Chen, Lama Darbelli, Chia-Lun Wu, Stefanie Perrier ... Show more

Brain, Volume 146, Issue 12, December 2023, Pages 5070–5085, https://doi.org/10.1093/brain/awad249

Published: 28 August 2023 **Article history**

Bringing rare and undiagnosed diseases out of the shadows

A new network will advance research and care for thousands of people suffering from a rare or undiagnosed disease

SOURCE: MUHC
February 29, 2024

https://rimuhc.ca/en/-/bringing-rare-and-undiagnosed-diseases-out-of-the-shadows

Sortir les maladies rares et non diagnostiquées de l'ombre

Un nouveau réseau fera progresser la recherche et les soins pour des milliers de personnes souffrant d'une maladie rare ou non diagnostiquée.

https://rimuhc.ca/fr/-/sortir-les-maladies-rares-et-non-diagnostiquees-de-l-ombre

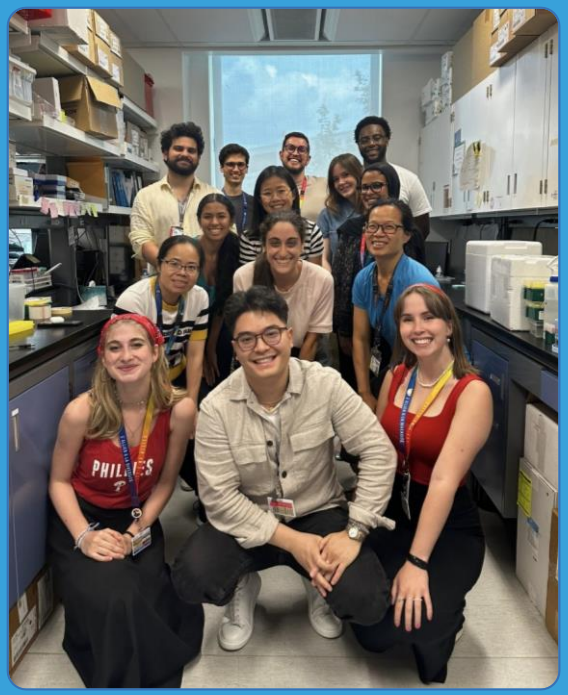
Follow us on social media for updates about our work!

MyeliNeuroGene Lab – Dr. Genevieve Bernard

@myelineurogene

MyeliNeuroGene Laboratory

Check out our website for more information!



MyeliNeuroGene LAB

"With my unique clinical and research expertise, my growing cohort of patients, international recognition, and my vast network of collaborators, I am strategically positioned to continue making this important and ambitious research program a success."

-Dr. Bernard

THANK YOU FOR YOUR CONTINUED SUPPORT!

For more information, please contact Josée Della Rocca,

jdel@mchf.com / 514-219-8949

The Montreal Children's Hospital Foundation
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